



# **STIC Search Report**

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**TO: Michael Borin**  
**Location: 12a01 / 12d01**  
**Wednesday, July 09, 2003**  
**Art Unit: 1631**  
**Phone: 305-4506**  
**Serial Number: 09 / 772538**

**From: Jan Delaval**  
**Location: Biotech-Chem Library**  
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### **Search Notes**

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97963

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# SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: M. BORIN (STN) Examiner #: 74104 Date: 07/02  
Art Unit: 1631 Phone Number 30 5-4506 Serial Number: 09/772538  
Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*  
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): \_\_\_\_\_

Earliest Priority Filing Date: \_\_\_\_\_

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search claims 1-9.  
For better understanding, I am  
attaching description of preferred  
embodiment

Thank you

M. Borin

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|---|------------------------|-----------------------------------|
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| Searcher Phone #: <u>4488</u>           | AA Sequence (#) _____  | Dialog _____                      |
| Searcher Location: _____                | Structure (#) _____    | Questel/Orbit _____               |
| Date Searcher Picked Up: <u>7/17/03</u> | Bibliographic <u>✓</u> | Dr. Link _____                    |
| Date Completed: <u>7/19/03</u>          | Litigation _____       | Lexis/Nexis _____                 |
| Searcher Prep & Review Time: _____      | Fulltext _____         | Sequence Systems _____            |
| Clerical Prep Time: <u>15</u>           | Patent Family _____    | WWW/Internet _____                |
| Online Time: <u>590</u>                 | Other _____            | Other (specify) _____             |

=> fil wpix  
 FILE 'WPIX' ENTERED AT 13:26:40 ON 09 JUL 2003  
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FILE LAST UPDATED: 7 JUL 2003 <20030707/UP>  
 MOST RECENT DERWENT UPDATE: 200343 <200343/DW>  
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=> d all abeq tech abex tot

L14 ANSWER 1 OF 7 WPIX (C) 2003 THOMSON DERWENT  
 AN 2000-182459 [16] WPIX  
 DNN N2000-134601 DNC C2000-057101  
 TI Identifying ligands for proteins, potentially useful as pharmaceuticals.  
 DC B04 D16 J04 S03  
 IN FROEMMEL, C; GOEDE, A; PREISSNER, R;  
 FROMMEL, C  
 PA (JERI-N) JERINI BIO TOOLS GMBH; (FROM-I) FROMMEL C; (GOED-I)  
 GOEDE A; (PREI-I) PREISSNER R  
 CYC 21  
 PI WO 2000004380 A1 20000127 (200016)\* DE 20p G01N033-53  
 RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE  
 W: JP US  
 DE 19831758 A1 20000203 (200018) G01N033-68  
 EP 1095272 A1 20010502 (200125) DE G01N033-53  
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE  
 US 2002048776 A1 20020425 (200233) G01N033-53 <--  
 ADT WO 2000004380 A1 WO 1999-EP4951 19990713; DE 19831758 A1 DE 1998-19831758  
 19980715; EP 1095272 A1 EP 1999-934689 19990713, WO 1999-EP4951 19990713;  
 US 2002048776 A1 US 2001-772538 20010129  
 FDT EP 1095272 A1 Based on WO 200004380  
 PRAI DE 1998-19831758 19980715  
 IC ICM G01N033-53; G01N033-68  
 ICS C07K001-00; C12Q001-00; G01N021-00; G01N033-542  
 AB WO 200004380 A UPAB: 20000330  
 NOVELTY - Determining ligands for proteins by determining the secondary  
 structure elements of the ligand which form the ligand binding site, is  
 new.  
 DETAILED DESCRIPTION - Determining ligands (I) for proteins (II)  
 comprises:  
 (i) determining secondary structure elements (SSE) of (I) that form  
 the ligand binding site;  
 (ii) partitioning the molecular surface of (I) into surface patches  
 (MSP);

(iii) identifying known areas (A) similar to the MSP that define the binding region, such that (A) possess a complementary neighbor element (B), co-ordinate transformation of (A) to (B) on a starting element at root mean square (rms) value below 2 Angstrom , and

(iv) estimating fitting of (I) according to local packing densities.

USE - The method is specifically used for determination of protein structures or for development of pharmaceuticals (claimed). Other applications for identified (I) are as diagnostic reagents, ligands for taste receptors (flavorings) and for affinity purification.

ADVANTAGE - The method determines (I) quickly and reliably.

Dwg.0/0

FS CPI EPI

FA AB

MC CPI: B11-C08; B12-K04E; D05-H09; D05-H10; D05-H13; J04-B01

EPI: S03-E14H4

TECH UPTX: 20000330

TECHNOLOGY FOCUS - BIOLOGY - Preferred Method: The outer surface of the secondary structure is determined, and outer surface elements that form contacts are selected as MSP. The similar known structures identified in the method are subjected to co-ordinate transformation, preferably to rms 1.5Angstrom, and then superimposed on the starting surface so that they lie on the atoms of the binding site. The best potential ligands are selected as lead compounds and/or are compared with known starting protein plus ligands.

Preferred ligands are determined as peptides of about 10 amino acids, then converted to peptidomimetics. (II) is an enzyme.

ABEX UPTX: 20000330

WIDER DISCLOSURE - Also disclosed is (I) determined by the new method and similar methods for identifying ligands that bind to RNA or DNA.

EXAMPLE - Starting from a binding site of an active subunit of the yeast proteosome, the secondary elements that define the binding site were determined. Five elements were detected, two of which formed the binding site. The exterior surface of these secondary elements was determined and the portion of the outer surface that made contacts (containing 12-22 atoms) was used to screen the DIP database for similar molecular surface patches (MSP). MSP with a minimum of 70% superimposition and root mean square value 1Angstrom were selected then superimposed on the starting surface. By co-ordinate transformation, reverse MSPs were formed, in the binding pocket, and assessed as potential ligands from their ability to fill the pocket and from whether the distances to atoms of the pocket were of correct size (local density). The best ligands were taken as lead compounds. A comparison of the 10 best ligands with a proteosome structure of an Archaeobacterium, with ligand attached, showed that the main chain of one ligand was identical with the known inhibitor of this proteosome.

L14 ANSWER 2 OF 7 WPIX (C) 2003 THOMSON DERWENT

AN 1997-385296 [35] WPIX

CR 2001-606375 [55]; 2002-414103 [23]

DNC C1997-123570

TI Computer system containing crystallographic coordinates of human osteogenic protein-1 - used for design of analogues with agonist activity, potentially useful for treating osteoporosis etc..

DC B04

IN GRIFFITH, D; KECK, P; RUEGER, D C; SAMPATH, K T; CARLSON, W D; GRIFFITH, D L

PA (CREA-N) CREATIVE BIOMOLECULES INC; (UYBR-N) UNIV BRANDEIS

CYC 21

PI WO 9726277 A2 19970724 (199735)\* EN 176p C07K014-51 <--

RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

W: AU CA JP

AU 9722449 A 19970811 (199747) C07K014-51

EP 876401 A2 19981111 (199849) EN C07K014-51

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE  
 JP 2000501744 W 20000215 (200019) 188p C07K014-495  
 AU 725295 B 20001012 (200055) C07K014-51  
 AU 2000053497 A 20001102 (200062)# C07K014-51  
 ADT WO 9726277 A2 WO 1997-US1071 19970122; AU 9722449 A AU 1997-22449  
 19970122; EP 876401 A2 EP 1997-905604 19970122, WO 1997-US1071 19970122;  
 JP 2000501744 W JP 1997-526303 19970122, WO 1997-US1071 19970122; AU  
 725295 B AU 1997-22449 19970122; AU 2000053497 A Div ex AU 1997-22449  
 19970122, AU 2000-53497 20000818  
 FDT AU 9722449 A Based on WO 9726277; EP 876401 A2 Based on WO 9726277; JP  
 2000501744 W Based on WO 9726277; AU 725295 B Previous Publ. AU 9722449,  
 Based on WO 9726277; AU 2000053497 A Div ex AU 725295  
 PRAI US 1996-589552 19960122; AU 2000-53497 20000818  
 IC ICM C07K014-495; C07K014-51  
 ICS C07K001-00; C07K007-06; C07K007-08; G06F017-00; G06F017-30;  
 G06F017-50  
 ICA C07B061-00  
 AB WO 9726277 A UPAB: 20020711  
 A novel computer system comprises: (a) a memory containing atomic X-ray  
 crystallographic coordinates defining at least part of human osteogenic  
 protein-1 (OP-1); and (b) a processor able to generate a molecular model  
 having the three-dimensional (3D) shape representative of at least part of  
 OP-1. Also new are: (1) production of a morphogenic analogue (I) with  
 OP-1-like activity by: (i) identifying a candidate compound having a 3D  
 shape corresponding to that of at least part of OP-1; then (ii) preparing  
 this compound; (2) a method for preparing an analogue (II) that modulates  
 an OP-1 mediated biological effect by using a similar process to (1) to  
 identify a compound with the 3D shape and solvent-accessible surface (SAS)  
 corresponding to those of OP-1; and (3) compounds identified by the  
 method.  
 USE - The computer system is used in the method to define potential  
 therapeutic agents. Typical applications of these are in proliferation of  
 progenitor cells and regeneration of damaged or diseased tissue (e.g.  
 osteoporosis or other bone-remodelling diseases) but more generally in any  
 situation where mimicking or agonism of OP-1 is required.  
 ADVANTAGE - The analogues identified have, compared with native OP-1,  
 better stability and/or solubility under physiological conditions;  
 improved tissue target specificity; better biodistribution and/or reduced  
 clearance rates. They may also lack an epitope or region recognised by a  
 cellular scavenging protein, or altered receptor binding characteristics.  
 Dwg.0/16  
 FS CPI  
 FA AB  
 MC CPI: B04-N02; B11-C09; B14-N01  
 L14 ANSWER 3 OF 7 WPIX (C) 2003 THOMSON DERWENT  
 AN 1996-433261 [43] WPIX  
 CR 1994-358467 [44]; 1998-052548 [05]  
 DNN N1996-365112  
 TI Model protein with variable regions three-dimensional structure computer  
 modelling - receiving relative positional information contg hi and phi  
 angle values between pairs of amino acids followed by establishing  
 position for first amino acid in variable region.  
 DC S03 T01  
 IN SRINIVASAN, S; SUDARSANAM, P  
 PA (IMMV) IMMUNEX CORP  
 CYC 1  
 PI US 5557535 A 19960917 (199643)\* 21p G01N037-00 <--  
 ADT US 5557535 A CIP of US 1993-55050 19930428, US 1994-234812 19940428  
 FDT US 5557535 A CIP of US 5453397  
 PRAI US 1994-234812 19940428; US 1993-55050 19930428  
 IC ICM G01N037-00  
 AB US 5557535 A UPAB: 19990511

The method involves receiving relative positional information between pairs of amino acids, followed by establishing a position for a first amino acid of the variable region. For each amino acid pair in the variable region, it requires generating a model position for the amino acids based on the received relative positional information for the pair of amino acids. The information includes  $\psi$  and  $\phi$  angle values between pairs of amino acids.

For each combination of pairs of amino acids in variable regions of a family of proteins, the method entails collecting the  $\psi$  and  $\phi$  angle values for each pair of amino acids and while the step of generating a model position bases the model position on one of the collected  $\psi$  and  $\phi$  angle values.

USE/ADVANTAGE - For modelling 3D structure of protein and sequence alignment between protein to be modelled and template protein. Minimizes short contacts and allows modelling proteins with weak sequence identity with template protein.

Dwg.2/10

FS EPI  
FA AB; GI  
MC EPI: S03-E14H5; T01-J15X

L14 ANSWER 4 OF 7 WPIX (C) 2003 THOMSON DERWENT  
AN 1996-139250 [14] WPIX  
DNN N1996-116692  
TI Vaccine and drug design - using coordinate axes with origin in binding site of receptor molecule and grid with mesh of resolution sufficient for low-energy amino acid locations and finding min. energy interaction energy position between amino acid and site.

DC S05 T01  
IN CORNETTE, J L; DELISI, C; ROSENFELD, R; SEZERMAN, U; VAJDA, S  
PA (UYBO-N) UNIV BOSTON

CYC 1  
PI US 5495423 A 19960227 (199614)\* 22p G06F017-50 <--  
ADT US 5495423 A US 1993-142597 19931025  
PRAI US 1993-142597 19931025  
IC ICM G06F017-50  
AB US 5495423 A UPAB: 19960405

A method for computing the conformation and location that a protein fragment will obtain in binding to the active site of a receptor is provided. The invention relates to both the computation of conformation and location of natural ligands within an active site and the design of artificial ligands with useful binding characteristics.

FS EPI  
FA AB  
MC EPI: S05-X; T01-J15X

L14 ANSWER 5 OF 7 WPIX (C) 2003 THOMSON DERWENT  
AN 1993-351641 [44] WPIX  
CR 1989-294634 [41]  
DNN N1993-271247 DNC C1993-156070  
TI New biologically active peptide with stabilised three-dimensional structure - mimics active site protein, useful e.g. as HIV or malaria vaccines, resistant to temp. and solvent changes.  
DC B04 D16 S03  
IN ARRHENIUS, T; CABEZA, E; CHIANG, L; SATTERTHWAIT, A C; CABEZAS, E  
PA (SCRI) SCRIPPS RES INST  
CYC 22  
PI WO 9321206 A1 19931028 (199344)\* EN 128p C07K001-00 <--  
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE  
W: AU CA FI JP NO  
AU 9339718 A 19931118 (199410) C07K001-00  
US 5807979 A 19980915 (199844) C07K007-54  
ADT WO 9321206 A1 WO 1993-US3032 19930331; AU 9339718 A AU 1993-39718

19930331; US 5807979 A Cont of US 1988-179160 19880408, Cont of US 1990-607645 19901029, CIP of US 1991-746064 19910812, Cont of US 1992-866040 19920408, Cont of US 1994-224059 19940407, US 1995-456424 19950601

FDT AU 9339718 A Based on WO 9321206

PRAI US 1993-33883 19930319; US 1992-866040 19920408; US 1988-179160 19880408; US 1990-607645 19901029; US 1991-746064 19910812; US 1994-224059 19940407; US 1995-456424 19950601

REP 5.Jnl.Ref; US 4642334; US 4777127

IC ICM C07K001-00; C07K007-54

ICS A61K037-02; A61K039-00; A61K039-395; C07K014-155; C07K015-00; C12N015-00; G01N033-53

AB WO 9321206 A UPAB: 19981104

New biologically active peptide (I) has a three-dimensionally stabilised configuration which mimics that of an active site of a natural biologically active protein. The configuration is stabilised by a covalently bound linking gp. which connects non-adjoining aminoacid residues in the peptide.

Partic. the linking gp. (which replaces an H bond) forms one of the structures (I), (II) or (III) of R = H or 1-6C alkyl; R1, R2 and R3 = H or 1-6C alkyl; R3 may also be a chain of 1-2000 aminoacids; R4 = any atom or gp. with the required configuration; m = 0-5; aa = aminoacid residue; n = 1-2000, esp. 3-30.

Pref. the aminoacid sequence and 3-D configuration of the active site of natural protein is determined, then a hydrogen bond identified which stabilises the structure. A peptide is synthesis (by standard methods) having (practically) the same sequence as the active site, then a covalent link is formed to join the atoms involves in the stabilising H bond. Partic. the covalent bond is formed by reaction with a divalent linker. More than one hydrogen bond can be replaced.

USE/ADVANTAGE - (I) are stabilised against changes in temp. and solvent, and against natural degradation processes, but retain the activity of (much larger) peptides. They can mimic a wide variety of pharmaceuticals, hormones, diagnostic reagents, vaccines, catalysts etc., e.g. epidermal growth factor, and HIV or malaria peptides. Configurationally restricted peptides should provide a more efficient immune response, producing antibodies with a binding pocket which closely complements the native protein surface.

Dwg.0/6

FS CPI EPI

FA AB; GI; DCN

MC CPI: B02-V02; B04-C01; B12-B03; B12-K04; D05-H07

EPI: S03-E14H4

L14 ANSWER 6 OF 7 WPIX (C) 2003 THOMSON DERWENT

AN 1993-045645 [05] WPIX

DNN N1993-034929 DNC C1993-020663

TI Characterising the three-dimensional structure of a protein - by analysing aminoacid residue positions and comparing with known protein structures.

DC B04 D16 T01

IN BOWIE, J U; EISENBERG, D; LUTHY, R

PA (REGC) UNIV CALIFORNIA

CYC 18

PI WO 9301484 A1 19930121 (199305)\* EN 56p G06F015-20 <--

RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE

W: AU CA JP

AU 9224082 A 19930211 (199321) G06F015-20

US 5436850 A 19950725 (199535) 23p G06F019-00

ADT WO 9301484 A1 WO 1992-US5773 19920710; AU 9224082 A AU 1992-24082 19920710; US 5436850 A Cont of US 1991-728640 19910711, US 1994-218685 19940328

FDT AU 9224082 A Based on WO 9301484

PRAI US 1991-728640 19910711; US 1994-218685 19940328

REP US 4704692; US 4717653; US 4853871; US 4881175; US 4908773; US 4939666; US 4946778; US 4976958; US 5087558

IC ICM G06F015-20; G06F019-00

ICS C12N015-00; C12Q001-68

AB WO 9301484 A UPAB: 19931119

Characterising the 3-dimensional(3-D) structure of a protein, comprises (a) determining, from the 3-D structure of the protein, values for a structural properties P1,P2....Pn for each amino acid residue position of the protein, (b) assigning each residue of the protein to one environment class based upon the values for the n structural properties P1,P2 ....Pn for the residue, thereby generating a 1-dimensional environment string comprising the environment class of each residue in the 3-D protein structure.

USE/ADVANTAGE - Permit the assignment of many amino acid sequences to known 3-D structures. Used partic. for screening structural analogues of a known protein sequence. The 3-D compatibility searches are able to detect structural relationships that may not be apparent by sequence similarity.

1/5

Dwg.1/5

FS CPI EPI

FA AB; GI

MC CPI: B04-B04A; B12-K04; D05-H09

EPI: T01-J10B2

ABEQ US 5436850 A UPAB: 19950905

The three-dimensional structure of a protein is characterised by determining values for n structural properties P1-Pn for each amino acid residue, and assigning each residue to one of a number of environmental classes based on the values to generate a one-dimensional environment string comprising the class of each residue. The data generated are input into a programmed computer which compares them to a database of other proteins of known structure and outputs analogous structures. The properties pref. include the total area of a residue side-chain buried by other protein atoms inaccessible to solvent, the fraction of the side-chain area covered by polar atoms or water, and the local secondary structure.

USE/ADVANTAGE - Partic. for identifying protein sequences which fold into a known three-dimensional structure. Relates a one-dimensional target sequence directly to known three-dimensional structures and effectively utilises information about the accommodation of sequence changes inherent in known structures.

Dwg.1/8

L14 ANSWER 7 OF 7 WPIX (C) 2003 THOMSON DERWENT

AN 1991-340015 [46] WPIX

DNN N1991-260465 DNC C1991-146838

TI 3-dimensional protein structure determining method - processing full sequence of aminoacid residues of protein using microprocessor for simulating folding of protein.

DC J04 S03 T01

IN SKOLNICK, J; KOLINSKI, A

PA (SCRI) SCRIPPS CLINIC & RES FOUND; (SCRI-N) SCRIPPS CLINIC & RE

CYC 20

PI WO 9116683 A 19911031 (199146)\* <--

RW: AT BE CH DE DK ES FR GB GR IT LU NL SE

W: AU CA FI JP NO

AU 9178837 A 19911111 (199207)

JP 05501324 W 19930311 (199315) 43p G06F015-20

PT 97480 A 19930531 (199325) G06F007-00

US 5265030 A 19931123 (199348) 74p G06F015-60

ADT JP 05501324 W JP 1991-509821 19910423, WO 1991-US2786 19910423; PT 97480 A PT 1991-97480 19910424; US 5265030 A Cont of US 1990-513918 19900424, Cont of US 1991-803678 19911203, US 1992-932282 19920819

FDT JP 05501324 W Based on WO 9116683



PRAI US 1990-513918 19900424

REP US 4704692; US 4853871; US 4881175; US 4908773; US 4939666; US 4985827

IC ICM G06F007-00; G06F015-20; G06F015-60

ICS G01N033-68; G06F015-42; G06F015-46

AB WO 9116683 A UPAB: 19931220

The method determines with a machine a three-dimensional structure of a protein or portion thereof including sidechains is claimed. A sequence of amino acid residues whose native tertiary structure is to be determined and local conformation preferences for respective residues of the sequence are specified.

A temp. is also specified, and a representation of an unfolded chain of the residues in three dimensions is automatically generated. Folding of the chain and interactions between all pairs of sidechains are simulated, and the representation of the tertiary structure displayed.

ADVANTAGE - Simulation of protein folding and prediction of tertiary structure are not only performed with greater success and accomplished faster than by many existing methods, but simulation itself becomes more manageable (tractable). @(109pp Dwg.No.3/16)@

FS CPI EPI

FA AB; GI

MC CPI: J04-C

EPI: S03-E14H1; T01-J07

ABEQ JP 05501324 W UPAB: 19930928

Determining three-dimensional structure of protein or portion including side chains, using machine is claimed. Sequence of amino acid residues whose native tertiary structure is to be determined and local conformation preferences for respective residues of the sequence are specified.

Temp. is also specified, and representation of unfolded chain of the residues in three dimensions is automatically generated. Folding of the chain and interactions between all pairs of side chains are simulated, and the representation of the tertiary structure displayed.

ADVANTAGE - Simulation of protein folding and prediction of tertiary structure are not only performed with greater success and accomplished faster than by many existing methods, but simulation itself becomes more manageable (tractable)

ABEQ US 5265030 A UPAB: 19940120

Three-dimensional structures of globular proteins are determined by a computer-based system which is based on a Monte Carlo dynamics technique with asymmetric Metropolis sampling criterion. A sequence of amino acid residues of a protein is specified and a 210 lattice structure is created for each amino acid of the protein. An unfolded conformation consisting of alpha-C backbone and side chains is represented spatially and successive likely tertiary conformations are selected, from which the lowest total-free-energy conformation is chosen. Coordinate set is created for display.

ADVANTAGE - Fast method of determining protein structures.

Dwg.15B/16

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FILE LAST UPDATED: 8 Jul 2003 (20030708/ED)

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L86 ANSWER 1 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:538255 HCAPLUS

DN 135:132768

TI **Computational** methods for generation of synthetic **ligands** based on the three dimensional **structure** of thyroid hormone receptor

IN Scanlan, Thomas S.; Baxter, John D.; Fletterick, Robert J.; Wagner, Richard L.; Kushner, Peter J.; Apriletti, James J.; West, Brian L.; Shiau, Andrew K.

PA Regents of the University of California, USA

SO U.S., 268 pp., Cont.-in-part of U.S. 6,236,946.

CODEN: USXXAM

DT Patent

LA English

IC ICM G06F019-00

ICS G06F017-00; C07G014-00

NCL 702022000

CC 2-7 (Mammalian Hormones)

Section cross-reference(s): 3, 6

FAN.CNT 3

|    | PATENT NO. | KIND | DATE     | APPLICATION NO. | DATE         |
|----|------------|------|----------|-----------------|--------------|
|    | -----      | ---- | -----    | -----           | -----        |
| PI | US 6266622 | B1   | 20010724 | US 1997-980115  | 19971126 <-- |
|    | CA 2240024 | AA   | 19970619 | CA 1996-2240024 | 19961213 <-- |
|    | US 6236946 | B1   | 20010522 | US 1996-764870  | 19961213 <-- |
|    | CA 2314096 | AA   | 19990603 | CA 1998-2314096 | 19981125 <-- |
|    | WO 9926966 | A2   | 19990603 | WO 1998-US25296 | 19981125 <-- |

WO 9926966 A3 20000120  
 W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9917999 A1 19990615 AU 1999-17999 19981125 <--

EP 1034184 A2 20000913 EP 1998-962849 19981125 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

BR 9815061 A 20011120 BR 1998-15061 19981125 <--

JP 2001524489 T2 20011204 JP 2000-522122 19981125 <--

PRAI US 1995-8540P P 19951213 <--

US 1995-8543P P 19951213 <--

US 1995-8606P P 19951214 <--

US 1996-764870 A2 19961213 <--

US 1997-980115 A 19971126 <--

WO 1998-US25296 W 19981125 <--

OS MARPAT 135:132768

AB The present invention provides new methods, particularly **computational** methods, and compns. for the generation of nuclear receptor synthetic **ligands** based on the three dimensional **structure** of nuclear receptors, particularly the thyroid receptor (TR). Also provided are crystals, nuclear receptor synthetic **ligands**, and related methods. The present invention provides for crystals of TR **ligand binding** domains with a **ligand** bound to the **ligand binding** domain (LBD), which provide excellent at. resoln. of the **amino acids** that interact with TR **ligand**, esp. thyroid receptor **ligands**. The three dimensional **model** of a TR LBD with a **ligand** bound reveals a previously unknown **structure** for nuclear receptors and shows that the **ligand** is bound in a water inaccessible **binding** cavity of the **ligand binding** domain of the TR. The present invention also includes a method for identifying a compd. capable of selectively modulating the activity of a TR isoform. Further included is a method for identifying agonist or antagonist **ligands** of a TR using the at. **coordinates** of a LBD in conjunction with a **computerized modeling** system. Also provided is a method of identifying a compd. that selectively modulates the activity of one type of nuclear receptor compared to other nuclear hormone receptors. Another aspect of the invention is a method for increasing the receptor selectivity of a compd. for a particular type of nuclear receptor. The invention finds use in the selection and characterization of **peptide**, peptidomimetic or synthetic compds. identified by the methods of the invention, particularly new lead compds. useful in treating disorders related to nuclear receptor-based deficiencies, including TR-related disorders.

ST thyroid hormone receptor **structure** synthetic **ligand**

IT **Protein motifs**

(LBD (**ligand-binding** domain); **computational** methods for generation of synthetic **ligands** based on three dimensional **structure** of thyroid hormone receptor)

IT **Computer application**

Drug **screening**

**Protein** sequences

(**computational** methods for generation of synthetic **ligands** based on three dimensional **structure** of thyroid hormone receptor)

IT Thyroid hormone receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BUU

- (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process); USES (Uses)  
 (computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT Hormone receptors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT Conformation  
 Crystallization  
 Secondary structure  
 (protein; computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT Structure-activity relationship  
 (thyroid hormone; computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT Thyroid hormone receptors  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process); USES (Uses)  
 (.alpha.; computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT Thyroid hormone receptors  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process); USES (Uses)  
 (.beta.; computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT 121939-99-9 351904-91-1  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (amino acid sequence; computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT 51-24-1, triac  
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
 (complexed with TR-.beta.; computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT 51-23-0P 140396-69-6P 192766-75-9P 192766-76-0P 192766-77-1P 192766-78-2P 192766-79-3P 192766-80-6P 350855-16-2P  
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)  
 (computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)
- IT 178877-78-6P  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
 (computational methods for generation of synthetic ligands based on three dimensional structure of thyroid hormone receptor)

- IT 1596-67-4, thyronine  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(**computational** methods for generation of synthetic  
**ligands** based on three dimensional **structure** of  
thyroid hormone receptor)
- IT 6893-02-3 91969-75-4 192766-82-8 350855-17-3  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(**computational** methods for generation of synthetic  
**ligands** based on three dimensional **structure** of  
thyroid hormone receptor)
- IT 351909-92-7  
RL: PRP (Properties)  
(unclaimed nucleotide sequence; **computational** methods for  
generation of synthetic **ligands** based on the three  
dimensional **structure** of thyroid hormone receptor)
- IT 100785-35-1 111518-64-0 112540-09-7 127187-77-3 130038-23-2, RNA  
formation factor RXR (human clone .lambda.XR3-1 isoform .alpha. reduced)  
149024-37-3 150474-29-6 170139-50-1 351909-86-9 351909-87-0  
351909-88-1 351909-89-2 351909-90-5 351909-91-6  
RL: PRP (Properties)  
(unclaimed **protein** sequence; **computational** methods  
for generation of synthetic **ligands** based on the three  
dimensional **structure** of thyroid hormone receptor)
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L86 ANSWER 2 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:284219 HCAPLUS

DN 134:305782

TI Crystallographic **structure** of the androgen receptor  
**ligand binding** domain and pharmacological applications

IN Weinmann, Roberto; Einspahr, Howard M.; Krystek, Stanley R., Jr.; Sack,  
 John S.; Salvati, Mark E.; Tokarski, John S.; Wang, Chihuei; Attar,  
 Ricardo M.

PA Bristol-Myers Squibb Company, USA

SO PCT Int. Appl., 83 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM G01N033-53

CC 2-2 (Mammalian Hormones)

Section cross-reference(s): 1, 75

FAN.CNT 1

|      | PATENT NO.      | KIND   | DATE         | APPLICATION NO. | DATE         |
|------|-----------------|--|--------------|-----------------|--------------|
| PI   | WO 2001027622   | A1   | 20010419     | WO 2000-US28495 | 20001013 <-- |
|      | W:              | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |              |                 |              |
|      | RW:             | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |              |                 |              |
|      | EP 1222459      | A1   | 20020717     | EP 2000-972172  | 20001013 <-- |
|      | R:              | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL   |              |                 |              |
|      | JP 2003511467   | T2   | 20030325     | JP 2001-530581  | 20001013 <-- |
| PRAI | US 1999-159394P | P  | 19991014 <-- |                 |              |
|      | WO 2000-US28495 | W  | 20001013     |                 |              |

AB The first crystal **structure** of the androgen receptor  
**ligand binding** domain has been detd. to 2.0  
**angstrom** resolu. Disclosed are the **coordinates** for the  
 crystal **structure**, and methods for detg. agonists, partial  
 agonists, antagonists, partial antagonists, and selective androgen

- receptors modulators of the androgen receptor.
- ST androgen receptor **ligand** domain crystal **structure**  
pharmacol
- IT Aging, animal  
(age-related disease treatment; crystallog. **structure** of  
androgen receptor **ligand binding** domain and  
pharmacol. applications)
- IT **Computer application**  
Crystal growth  
Crystal **structure**  
    **Drug design**  
    **Drug screening**  
Mammal (Mammalia)  
    **Molecular modeling**  
    **Molecular recognition**  
    **Protein sequences**  
Rat  
    (crystallog. **structure** of androgen receptor **ligand**  
    **binding** domain and pharmacol. applications)
- IT Androgen receptors  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); THU (Therapeutic use); BIOL (Biological study); PROC  
(Process); USES (Uses)  
    (crystallog. **structure** of androgen receptor **ligand**  
    **binding** domain and pharmacol. applications)
- IT **Ligands**  
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
(Biological study)  
    (crystallog. **structure** of androgen receptor **ligand**  
    **binding** domain and pharmacol. applications)
- IT Sexual behavior  
(impotence, treatment of; crystallog. **structure** of androgen  
receptor **ligand binding** domain and pharmacol.  
applications)
- IT Prostate gland  
(neoplasm, inhibitors; crystallog. **structure** of androgen  
receptor **ligand binding** domain and pharmacol.  
applications)
- IT Antitumor agents  
(prostate gland; crystallog. **structure** of androgen receptor  
**ligand binding** domain and pharmacol. applications)
- IT **Conformation**  
    **Helix (conformation)**  
    (**protein**; crystallog. **structure** of androgen  
    receptor **ligand binding** domain and pharmacol.  
    applications)
- IT Information systems  
(storage; crystallog. **structure** of androgen receptor  
**ligand binding** domain and pharmacol. applications)
- IT Osteoporosis  
(therapeutic agents; crystallog. **structure** of androgen  
receptor **ligand binding** domain and pharmacol.  
applications)
- IT 335182-97-3D, 672-917-Androgen receptor (rat), mutants are claimed  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); THU (Therapeutic use); BIOL (Biological study); PROC  
(Process); USES (Uses)  
    (**amino acid** sequence; crystallog. **structure**  
    of androgen receptor **ligand binding** domain and  
    pharmacol. applications)
- IT 521-18-6D, Dihydrotestosterone, complexes with androgen receptor  
**ligand binding** domain  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP



(Properties); THU (Therapeutic use); BIOL (Biological study); PROC  
(Process); USES (Uses)

(crystallog. **structure** of androgen receptor **ligand**  
**binding** domain and pharmacol. applications)

IT 335190-37-9 335190-38-0

RL: PRP (Properties)

(unclaimed nucleotide sequence; crystallog. **structure** of the  
androgen receptor **ligand binding** domain and  
pharmacol. applications)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

- (1) Claussner; US 5434176 A 1995 HCAPLUS
- (2) Dedhar; US 5854202 A 1998 HCAPLUS
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HCAPLUS
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L86 ANSWER 3 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 2000:145057 HCAPLUS

DN 132:205136

TI Methods and systems for predicting **protein** function

IN Skolnick, Jeffrey; Fetrow, Jacquelyn S.

PA The Scripps Research Institute, USA

SO PCT Int. Appl., 173 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12Q001-00

ICS C12Q001-26; C12Q001-37; C12Q001-44; C12N009-00; C12N009-02;  
C12N009-14; C12N009-22; C12N009-48; C12N009-50; G01N031-00;  
G01N033-00; A61K038-00; C07K001-00

CC 9-16 (Biochemical Methods)

Section cross-reference(s): 3, 6, 7

FAN.CNT 2

|      | PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE         |
|------|---|------|----------|-----------------|--------------|
| PI   | WO 2000011206   | A1   | 20000302 | WO 1999-US11913 | 19990527 <-- |
|      | W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,    |      |          |                 |              |
|      | DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,       |      |          |                 |              |
|      | JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,       |      |          |                 |              |
|      | MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,       |      |          |                 |              |
|      | TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,       |      |          |                 |              |
|      | MD, RU, TJ, TM  |      |          |                 |              |
|      | RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,   |      |          |                 |              |
|      | ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,       |      |          |                 |              |
|      | CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG                            |      |          |                 |              |
|      | CA 2340284  | AA   | 20000302 | CA 1999-2340284 | 19990527 <-- |
|      | AU 9942187  | A1   | 20000314 | AU 1999-42187   | 19990527 <-- |
|      | EP 1108055  | A1   | 20010620 | EP 1999-926014  | 19990527 <-- |
|      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,    |      |          |                 |              |
|      | IE, FI  |      |          |                 |              |
|      | JP 2002523057   | T2   | 20020730 | JP 2000-566458  | 19990527 <-- |
|      | US 2001034580   | A1   | 20011025 | US 2001-839821  | 20010420 <-- |
| PRAI | US 1998-99300P  | P    | 19980825 | <--             |              |
|      | US 1999-120311P   | P    | 19990216 | <--             |              |
|      | US 1999-322067  | A3   | 19990527 | <--             |              |
|      | WO 1999-US11913   | W    | 19990527 | <--             |              |
| AB   | The present invention concerns methods and systems for predicting the |      |          |                 |              |

biol. function(s) of **proteins**. The invention is based on the development of functional site descriptors for discrete **protein** biol. functions. Functional site descriptors are geometric representations of **protein** functional sites in three-dimensional space, and can also include addnl. parameters, for example, **conformational** information. Following their development, one or more functional site descriptors (for one or more different biol. functions) are used to probe **protein structures** to det. if such **structures** contain the functional sites described by the corresponding functional site descriptors. If so, the **protein(s)** contg. the functional site(s) are predicted to have the corresponding biol. function(s). In preferred embodiments, a library of functional site descriptors is used to probe inexact **protein structures** derived by **computational** methods from **amino acid** sequence information to predict the biol. function(s) of such sequences and of the gene(s) encoding the same. The Escherichia coli genome was **screened** by the sequence-to-**structure-to-function** paradigm to identify **proteins** having disulfide oxidoreductase activity.

- ST **protein** function prediction system; sequence library functional site descriptor **protein**; **computer** program  
**protein** function prediction; genome sequence **screening**  
disulfide oxidoreductase **protein**
- IT Mycoplasma genitalium  
(algorithm in functional anal. of; methods and systems for predicting **protein** function)
- IT **Ligands**  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(binding domain for, as functional site descriptor; methods and systems for predicting **protein** function)
- IT **Enzyme** functional sites  
(cofactor-binding, domain for, as functional site descriptor; methods and systems for predicting **protein** function)
- IT Thioredoxins  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(disulfide oxidoreductase activity of, functional site descriptors of; methods and systems for predicting **protein** function)
- IT **Molecular association**  
(domain for, as functional site descriptor; methods and systems for predicting **protein** function)
- IT Haemophilus influenzae  
Methanococcus jannaschii  
(functional anal. of genome of, for **proteins** having thiol/disulfide oxidoreductase activity; methods and systems for predicting **protein** function)
- IT Escherichia coli  
(functional **screening** of genome of, for disulfide oxidoreductase activity; methods and systems for predicting **protein** function)
- IT Genome  
(functional **screening** of, of Escherichia coli, for disulfide oxidoreductase activity; methods and systems for predicting **protein** function)
- IT Antigens  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(functional site descriptor for **protein** domain binding to; methods and systems for predicting **protein** function)
- IT **Proteins**, specific or class

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (glutaredoxins, disulfide oxidoreductase activity of, functional site descriptors of; methods and systems for predicting **protein** function)

IT **Algorithm**

Computer program

Computers

DNA sequences

Enzyme functional sites

NMR (nuclear magnetic resonance)

Protein folding

Protein motifs

Protein sequences

Simulation and Modeling, biological

Structure-activity relationship

(methods and systems for predicting **protein** function)

IT **Proteins, general, properties**

RL: PRP (Properties)

(methods and systems for predicting **protein** function)

IT **Peptide library**

(of functional site descriptors; methods and systems for predicting **protein** function)

IT **Gene**

RL: PRP (Properties)

(open reading frame, functional **screening** of, of Escherichia coli, for disulfide oxidoreductase activity; methods and systems for predicting **protein** function)

IT **Animal**

Canidae

Cattle

Felidae

Horse (Equus caballus)

Mammal (Mammalia)

Plant (Embryophyta)

Prokaryote

Sheep

Swine

Virus

(**protein** of; methods and systems for predicting **protein** function)

IT **Secondary structure**

**Tertiary structure**

(**protein**; methods and systems for predicting **protein** function)

IT **Saccharomyces cerevisiae**

(**proteins** of, disulfide oxidoreductase functional site descriptor testing against; methods and systems for predicting **protein** function)

IT **Toxins**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (ribo-, T1 RNase functional site descriptor testing against; methods and systems for predicting **protein** function)

IT **Information systems**

(searching; methods and systems for predicting **protein** function)

IT **Enzyme functional sites**

(substrate-**binding**, domain for, as functional site descriptor; methods and systems for predicting **protein** function)

IT **Crystallography**

(x-ray; methods and systems for predicting **protein** function)

- IT 9013-93-8, Phospholipase 9026-12-4 9068-62-6, Disulfide reductase  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(functional site descriptor for; methods and systems for predicting **protein** function)
- IT 52-90-4, Cysteine, properties 56-40-6, Glycine, properties 56-41-7, L-Alanine, properties 56-45-1, Serine, properties 56-84-8, Aspartic acid, properties 56-85-9, Glutamine, properties 56-86-0, L-Glutamic acid, properties 56-87-1, L-Lysine, properties 60-18-4, Tyrosine, properties 61-90-5, Leucine, properties 63-68-3, Methionine, properties 63-91-2, Phenylalanine, properties 70-47-3, Asparagine, properties 71-00-1, Histidine, properties 72-18-4, Valine, properties 72-19-5, Threonine, properties 73-22-3, Tryptophan, properties 73-32-5, Isoleucine, properties 74-79-3, Arginine, properties 147-85-3, Proline, properties  
RL: PRP (Properties)  
(in functional site descriptor; methods and systems for predicting **protein** function)
- IT 9001-62-1, Lipase  
RL: PRP (Properties)  
(**structure** of, in building consensus active site **structure** for .alpha./.beta. hydrolases; methods and systems for predicting **protein** function)
- IT 94587-93-6 117698-18-7 132052-53-0, .alpha.-Sarcin (Aspergillus giganteus strain MDH18894 precursor reduced) 136073-15-9, Restrictocin (Aspergillus restrictus clone pFB39c1 precursor reduced) 172142-71-1 180256-67-1 260345-59-3 260345-60-6 260345-61-7 260345-62-8 260345-63-9 260345-64-0  
RL: PRP (Properties)  
(unclaimed sequence; methods and systems for predicting **protein** function)
- IT 9027-41-2, Hydrolase  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(.alpha./.beta.-**fold** contg., functional site descriptor for; methods and systems for predicting **protein** function)
- RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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- (1) Biswanadhan; Biochemistry 1991, V30, P11164
  - (2) Chao; CABIOS 1992, V8(5), P481 HCAPLUS
  - (3) Clarke; Science 1988, V240, P521 HCAPLUS
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L86 ANSWER 4 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 2000:68632 HCAPLUS

DN 132:105024

TI Determination of ligands for proteins via modeling of molecular surface patches

IN Frommel, Cornelius; Preissner, Robert; Goede, Andrean

PA Jerini Bio Tools G.m.b.H., Germany

SO PCT Int. Appl., 21 pp.

CODEN: PIXXD2

DT Patent

LA German

IC ICM G01N033-53  
ICS C07K001-00  
CC 9-16 (Biochemical Methods)  
Section cross-reference(s): 1, 6  
FAN.CNT 1

|      | PATENT NO.   | KIND | DATE     | APPLICATION NO.  | DATE         |
|------|--|------|----------|------------------|--------------|
| PI   | WO 2000004380  | A1   | 20000127 | WO 1999-EP4951   | 19990713 <-- |
|      | W: JP, US  |      |          |                  |              |
|      | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |      |          |                  |              |
|      | DE 19831758  | A1   | 20000203 | DE 1998-19831758 | 19980715 <-- |
|      | EP 1095272   | A1   | 20010502 | EP 1999-934689   | 19990713 <-- |
|      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI  |      |          |                  |              |
|      | US 2002048776  | A1   | 20020425 | US 2001-772538   | 20010129 <-- |
| PRAI | DE 1998-19831758   | A    | 19980715 | <--              |              |
|      | WO 1999-EP4951   | W    | 19990713 | <--              |              |

AB The invention relates to a method for detg. **ligands** for **proteins**. Said method comprises detg., by means of **secondary structural** elements of a given **protein** which form the **binding site**, **mol. surface patches** (MSP) which are compared with known **mol. surface patches** with **ligand**. The method is used for drug **design**, in biotechnol. for finding affinity purifn. **ligands**, in the food industry for the research of flavoring compds. in relation to taste receptors.

ST **protein ligand binding drug design**  
affinity purifn flavoring material

IT Affinity chromatography  
Computer application  
Databases  
Drug design  
Flavoring materials  
Molecular association  
Molecular recognition  
Molecular surface  
Protein motifs  
Simulation and Modeling, physicochemical  
(detn. of ligands for proteins via modeling of mol. surface patches)

IT Taste receptors  
RL: FFD (Food or feed use); BIOL (Biological study); USES (Uses)  
(detn. of ligands for proteins via modeling of mol. surface patches)

IT **Enzymes**, properties  
RL: PRP (Properties)  
(detn. of ligands for proteins via modeling of mol. surface patches)

IT **Ligands**  
RL: PRP (Properties)  
(detn. of ligands for proteins via modeling of mol. surface patches)

IT **Proteins**, general, properties  
RL: PRP (Properties)  
(detn. of ligands for proteins via modeling of mol. surface patches)

IT **Peptides**, properties  
RL: PRP (Properties)  
(ligands; detn. of ligands for proteins via modeling of mol. surface patches)

IT **Conformation**

**Secondary structure**

(protein; detn. of ligands for proteins  
via modeling of mol. surface  
patches)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

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L86 ANSWER 5 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 2000:53689 HCAPLUS

DN 132:106951

TI Isolated amphiphilic **peptides** derived from the cytoplasmic tail  
of viral envelope **proteins**

IN Rozenberg, Yanina; Anderson, W. French

PA University of Southern California, USA

SO PCT Int. Appl., 83 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07K014-00

CC 15-2 (Immunochemistry)

Section cross-reference(s): 3, 63

FAN.CNT 1

|      | PATENT NO.     | KIND | DATE   | APPLICATION NO. | DATE         |
|------|----------------|------|--|-----------------|--------------|
| PI   | WO 2000002909  | A2   | 20000120   | WO 1999-IB1261  | 19990708 <-- |
|      | WO 2000002909  | A3   | 20000504   |                 |              |
|      | W:             |      | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM |                 |              |
|      | RW:            |      | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |                 |              |
|      | CA 2333855     | AA   | 20000120   | CA 1999-2333855 | 19990708 <-- |
|      | AU 9943869     | A1   | 20000201   | AU 1999-43869   | 19990708 <-- |
|      | EP 1093519     | A2   | 20010425   | EP 1999-926703  | 19990708 <-- |
|      | R:             |      | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI   |                 |              |
|      | US 2002058020  | A1   | 20020516   | US 2001-756250  | 20010108 <-- |
| PRAI | US 1998-112544 | A    | 19980709   | <--             |              |
|      | WO 1999-IB1261 | W    | 19990708   | <--             |              |

AB An isolated **peptide** comprising an **amino acid** sequence derived from a viral envelope **protein**, wherein at least a portion of the **amino acid** sequence is located within the cytoplasmic tail or membrane-spanning region of a viral envelope **protein**. Such **peptides** are amphiphilic in nature, provide for the destabilization of membranes, and facilitate the entry of viral particles into cells and the efficient formation of viral particles. The **peptides** may, in another embodiment, be attached to the viral membrane, along with a targeting **polypeptide**, as part of an artificial viral envelope **protein**.

ST virus retrovirus cytoplasmic envelope **peptide** liposome

- IT **Algorithm**  
(Chou, Fasman and Rose; amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT **Algorithm**  
(Kyte and Doolittle; amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT Biomarkers (biological responses)  
Circular dichroism  
DNA sequences  
Drug targeting  
ESR (electron spin resonance)  
Gene targeting  
Liposomes  
Murine leukemia virus  
Protein sequences  
Retroviral vectors  
Retroviridae  
Virus  
Virus vectors  
alpha.-Helix  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT Polynucleotides  
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT **Ligands**  
gag **proteins**  
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT Envelope **proteins**  
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT **Peptides**, biological studies  
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT **Enzymes**, biological studies  
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(gene pol; amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT Drug delivery systems  
(liposomes; amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT Animal cell  
Animal cell line  
(pre-packaging; amphiphilic **peptides** of viral envelope

- proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT Membrane, biological  
(viral; amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT 255719-95-0, Ilnrlvqfvkdrisvvqal **peptide+** 255719-96-1, Lkvlttglpalms **peptide+** 255719-97-2, Lkvlttglpalmswi **peptide+**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT 255859-47-3 255859-48-4  
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT 26853-31-6, POPC 81490-05-3, POPG  
RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- IT 255859-93-9  
RL: PRP (Properties)  
(nucleotide sequence; amphiphilic **peptides** of viral envelope **proteins** and encoding polynucleotides for anal. and targeting therapeutic **peptides** and gene)
- L86 ANSWER 6 OF 26 HCAPLUS COPYRIGHT 2003 ACS  
AN 2000:5177 HCAPLUS  
DN 132:136203  
TI Fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-**ligand binding**  
AU Burrows, Louise; Clark, Katherine; Mould, A. Paul; Humphries, Martin J.  
CS Wellcome Trust Centre for Cell-Matrix Research, University of Manchester, Manchester, M13 9PT, UK  
SO Biochemical Journal (1999), 344(2), 527-533  
CODEN: BIJOAK; ISSN: 0264-6021  
PB Portland Press Ltd.  
DT Journal  
LA English  
CC 15-3 (Immunochemistry)  
Section cross-reference(s): 6  
AB The high-affinity interaction of integrin .alpha.5.beta.1 with the central cell-**binding** domain of fibronectin requires both the Arg-Gly-Asp (RGD) sequence (in the tenth type III repeat) and a **second** site Pro-His-Ser-Arg-Asn (PHSRN) in the adjacent ninth type III repeat, which synergizes with RGD. Arg-Arg-Glu-Thr-Ala-Trp-Ala (RRETAWA) is a novel peptidic **ligand** for .alpha.5.beta.1, identified by phage display, which blocks .alpha.5.beta.1-mediated cell adhesion to fibronectin. A key question is the location of the **binding** sites for these **ligand** sequences within the integrin. In this study we have identified residues that form part of the epitopes of three inhibitory anti-.alpha.5 monoclonal antibodies (mAbs): 16, PlD6 and SNAKA52. These mAbs have distinct functional properties. MAb 16 blocks the **recognition** of RGD and RRETAWA, whereas PlD6 blocks **binding** to the synergy sequence. The **binding** of SNAKA52 is inhibited by anti-.beta.1 mAbs, indicating that its epitope is close to



the interface between the .alpha. and .beta. subunits. Residues in human .alpha.5 were replaced with the corresponding residues in mouse .alpha.5 by site-directed mutagenesis; wild-type or mutant human .alpha.5 was expressed on the **surface** of .alpha.5-deficient Chinese hamster ovary cells. MAb **binding** was assessed by flow cytometry and by adhesion to the central cell-**binding** domain of fibronectin or RRETAWA by cell attachment assay. All three epitopes were located to different putative loops in the N-terminal domain of .alpha.5. As expected, disruption of these epitopes had no effect on **ligand recognition** by .alpha.5.beta.1. The locations of these epitopes are consistent with the .beta.-propeller **model** for integrin .alpha.-subunit **structure** and allow us to propose a topol. image of the integrin-**ligand** complex.

- ST epitope mapping monoclonal Ig integrin **ligand binding**;  
fibronectin integrin **binding conformation** propeller  
**model**
- IT Animal cell line  
(CHO; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody  
epitopes that differentially affect integrin-fibronectin **ligand  
binding**)
- IT Immunoglobulins  
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU  
(Biological study, unclassified); PRP (Properties); BIOL (Biological  
study); PREP (Preparation); PROC (Process)  
(G, monoclonal; fine mapping of inhibitory anti-.alpha.5 monoclonal  
antibody epitopes that differentially affect integrin-fibronectin  
**ligand binding**)
- IT Extracellular matrix  
**Molecular association**  
**Molecular topology**  
**Repeat motifs (protein)**  
(fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes  
that differentially affect integrin-fibronectin **ligand  
binding**)
- IT **Peptides, biological studies**  
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU  
(Biological study, unclassified); PRP (Properties); BIOL (Biological  
study); PREP (Preparation); PROC (Process)  
(fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes  
that differentially affect integrin-fibronectin **ligand  
binding**)
- IT Fibrinogens  
**Ligands**  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); BIOL (Biological study); PROC (Process)  
(fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes  
that differentially affect integrin-fibronectin **ligand  
binding**)
- IT **Secondary structure**  
(fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes  
that differentially affect integrin-fibronectin **ligand  
binding** and human and mouse blades 2 and 3 of integrin  
.beta.-propeller **model**)
- IT **Molecular modeling**  
(fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes  
that differentially affect integrin-fibronectin **ligand  
binding** and human and mouse blades 2 and 3 of .beta.-propeller  
**model**)
- IT **Protein sequences**  
(homol.; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody  
epitopes that differentially affect integrin-fibronectin **ligand  
binding** and human and mouse blades 2 and 3 of .beta.-propeller  
**model**)

- IT Epitopes  
(mapping; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-fibronectin **ligand binding**)
- IT Conformation  
(**protein**, .beta.-propeller **model**; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-fibronectin **ligand binding** and human and mouse blades 2 and 3 of integrin .beta.-propeller **model**)
- IT Mutagenesis  
(site-directed; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-fibronectin **ligand binding** studied by)
- IT Integrins  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(.alpha.5.beta.1; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-fibronectin **ligand binding**)
- IT Conformation  
(.beta.-strand, seven bladed .beta.-propeller; fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-fibronectin **ligand binding**)
- IT 99896-85-2P 158622-13-0P 168179-93-9P  
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process)  
(fine mapping of inhibitory anti-.alpha.5 monoclonal antibody epitopes that differentially affect integrin-fibronectin **ligand binding**)

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L86 ANSWER 7 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:641074 HCAPLUS

DN 131:282013

TI Methods and compounds for modulating nuclear receptor activity

IN Shiau, Andrew; Kushner, Peter J.; Agard, David A.; Greene, Geoffrey L.

PA University of California, USA; Arch Development Corp.

SO PCT Int. Appl., 207 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM G01N033-48

CC 2-1 (Mammalian Hormones)

Section cross-reference(s): 1

FAN.CNT 2

|      | PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE         |
|------|--|------|----------|-----------------|--------------|
| PI   | WO 9950658   | A2   | 19991007 | WO 1999-US6937  | 19990330 <-- |
|      | W: AU, CA, JP, KR, US  |      |          |                 |              |
|      | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |      |          |                 |              |
|      | CA 2324060   | AA   | 19991007 | CA 1999-2324060 | 19990330 <-- |
|      | AU 9934571   | A1   | 19991018 | AU 1999-34571   | 19990330 <-- |
|      | CA 2323575   | AA   | 19991125 | CA 1999-2323575 | 19990330 <-- |
|      | WO 9960014   | A2   | 19991125 | WO 1999-US6899  | 19990330 <-- |
|      | WO 9960014   | A3   | 20000518 |                 |              |
|      | WO 9960014   | C2   | 20020829 |                 |              |
|      | W: AU, CA, JP, KR  |      |          |                 |              |
|      | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |      |          |                 |              |
| EP   | 1068529  | A2   | 20010117 | EP 1999-944980  | 19990330 <-- |
|      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI  |      |          |                 |              |
| EP   | 1144997  | A2   | 20011017 | EP 1999-916206  | 19990330 <-- |
| EP   | 1144997  | A3   | 20020828 |                 |              |
|      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI  |      |          |                 |              |
| US   | 2002061539   | A1   | 20020523 | US 1999-281717  | 19990330 <-- |
| JP   | 2002516983   | T2   | 20020611 | JP 2000-541516  | 19990330 <-- |
| PRAI | US 1998-79956P   | P    | 19980330 | <--             |              |
|      | US 1998-113014P  | P    | 19981216 | <--             |              |
|      | US 1998-113146P  | P    | 19981216 | <--             |              |
|      | US 1998-79965P   | P    | 19980330 | <--             |              |
|      | WO 1999-US6899   | W    | 19990330 | <--             |              |
|      | WO 1999-US6937   | W    | 19990330 | <--             |              |

AB The present invention relates to methods and agonist/antagonist compds. for modulating nuclear receptor activity, and nuclear receptor **ligand binding**. The invention includes a method for identifying residues comprising a **ligand binding** domain for a nuclear receptor of interest. Also included in a method of identifying agonists and/or antagonists that **bind** to the **ligand binding** domain of the nuclear receptors, and the estrogen receptor in particular. The invention is exemplified by identification and manipulation of the **ligand binding** domain of the estrogen receptor and compds. that **bind** to this site. The methods can be applied to other nuclear receptors including TR, GR and PR.

ST estrogen nuclear receptor **ligand screening**

IT **Bond**

(hydrophobic; **screening** for compds. modulating nuclear

- receptor activity)
- IT **Helix (conformation)**  
(**protein; screening** for compds. modulating nuclear receptor activity)
- IT Peroxisome  
(receptors; **screening** for compds. modulating nuclear receptor activity)
- IT Combinatorial library  
**Computer application**  
**Crystal structure**  
**Dipole**  
**Drug screening**  
**Hydrogen bond**  
**Molecular association**  
**Molecular cloning**  
**Molecular modeling**  
Peptidomimetics  
**Protein sequences**  
(**screening** for compds. modulating nuclear receptor activity)
- IT Androgen receptors  
Estrogen receptors  
Glucocorticoid receptors  
**Ligands**  
Mineralocorticoid receptors  
Nuclear receptors  
**Peptides**, biological studies  
Progesterone receptors  
Retinoid receptors  
Thyroid hormone receptors  
Vitamin D receptors  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(**screening** for compds. modulating nuclear receptor activity)
- IT Information systems  
(storage; **screening** for compds. modulating nuclear receptor activity)
- IT **Bond**  
(van der Waals; **screening** for compds. modulating nuclear receptor activity)
- IT 61-90-5, Leucine, biological studies 63-68-3, Methionine, biological studies 71-00-1, Histidine, biological studies  
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)  
(of human estrogen receptor .alpha.; **screening** for compds. modulating nuclear receptor activity)
- IT 50-28-2, 17.beta.-Estradiol, biological studies 56-53-1, Diethylstilbestrol 84-16-2, Mesohehexestrol 143-50-0, Kepone 479-13-0, Coumestrol 789-02-6 1972-08-3, .DELTA.9-Thc 10540-29-1, Tamoxifen 17924-92-4, Zearalenone 34816-55-2, Moxestrol 84449-90-1, Raloxifene 98007-99-9 155701-61-4, Gw5638 182167-03-9, Em800 205128-72-9  
245122-98-9 245122-99-0 245123-00-6 245123-01-7 245123-02-8  
245123-03-9 245123-04-0 245123-05-1 245123-06-2 245123-07-3  
245123-08-4 245123-09-5 245676-26-0 245676-32-8 245676-38-4  
245676-43-1 245676-45-3 245676-46-4 245676-47-5 245676-49-7  
245676-54-4 246236-26-0  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(**screening** for compds. modulating nuclear receptor activity)
- IT 245742-95-4, PN: W09950658 SEQID: 1 unclaimed **protein**  
245742-96-5, PN: W09950658 SEQID: 2 unclaimed **protein**  
RL: PRP (Properties)  
(unclaimed **protein** sequence; methods and compds. for modulating nuclear receptor activity)

L86 ANSWER 8 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:353941 HCAPLUS

DN 131:181313

TI **Protein surface recognition**

AU Salvatella, X.; Haack, T.; Gairi, M.; De Mendoza, J.; Peczuh, M. W.;  
Hamilton, A. D.; Giralt, E.

CS Departament de Quimica Organica, Universitat de Barcelona, Barcelona,  
08028, Spain

SO NATO ASI Series, Series C: Mathematical and Physical Sciences (  
1999), 526(NMR in Supramolecular Chemistry), 267-280  
CODEN: NSCSDW; ISSN: 0258-2023

PB Kluwer Academic Publishers

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB The development of a **ligand** for **mol.**

**recognition** of the external **protein surface** is  
a challenging task. Difficulties arise because of the high degree of  
solvation and the hydrophilic character of **protein**  
**surfaces**, where intermol. interactions such as hydrogen bonds and  
electrostatic forces play a key role. A tetraguanidinium compd. was  
studied for its ability to be used as a receptor for **recognition**  
of **peptides** or **proteins** with anionic helical  
**structures**. The **recognition** depends primarily on two  
factors, helicity of the **protein** and accessibility of neg.  
charged residues (aspartate or glutamate) at crit. positions to interact  
with the **ligand**. A search of the Brookhaven **Protein**  
Data Bank yielded 31 entries that contained the relevant features. Visual  
inspection of these **protein structures** narrowed the  
possible hits to 10, which were considered good candidates for  
**recognition** and were studied using a more systematic approach.  
For most of these **proteins**, the accessibility and helicity of  
the anionic paths were too low to expect any **binding** to the  
tetraguanidinic receptor. One exception was the p53 tumor suppressor  
**protein**, which was chosen to assess the **surface-**  
**binding** properties of the tetraguanidinic receptor.

ST **protein surface recognition** tetraguanidinium  
receptor

IT Annexins

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); BIOL (Biological study); PROC (Process)  
(IV; **protein surface recognition** by a  
tetraguanidinium receptor **ligand**)

IT Carboxyl group  
(accessibility; **protein surface recognition**  
by a tetraguanidinium receptor **ligand**)

IT **Molecular recognition**

**.alpha.-Helix**

(**protein surface recognition** by a  
tetraguanidinium receptor **ligand**)

IT **Proteins**, general, biological studies  
p53 (**protein**)

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); BIOL (Biological study); PROC (Process)  
(**protein surface recognition** by a  
tetraguanidinium receptor **ligand**)

IT Myosins

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
(Properties); BIOL (Biological study); PROC (Process)  
(regulatory domain; **protein surface**  
**recognition** by a tetraguanidinium receptor **ligand**)

IT Transcription factors

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(repressors, of primer of DNA replication; **protein surface recognition** by a tetraguanidinium receptor ligand)

IT 239136-49-3

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(p53 tumor suppressor **protein model peptide**; **protein surface recognition** by a tetraguanidinium receptor ligand)

IT 9040-57-7, Ribonucleotide reductase

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(**protein** subunit R2; **protein surface recognition** by a tetraguanidinium receptor ligand)

IT 9001-04-1, Pyruvate decarboxylase 9028-56-2, 3.alpha.-Hydroxysteroid dehydrogenase 9031-26-9, Lysyl-tRNA synthetase 37329-68-3, Procarboxypeptidase B 118901-79-4, Scytalone dehydratase 194547-39-2

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(**protein surface recognition** by a tetraguanidinium receptor ligand)

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L86 ANSWER 9 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:193896 HCAPLUS

DN 130:207008

TI Method and system for **protein modeling**

IN Srinivasan, Subhashini; Sudarsanam, Padmanaban

PA Immunex Corporation, USA

SO U.S., 29 pp., Cont.-in-part of U.S. 5,453,937.

CODEN: USXXAM

DT Patent

LA English

IC ICM G06F019-00

ICS C07K005-00; C07K014-00

NCL 702022000

CC 9-16 (Biochemical Methods)

Section cross-reference(s): 6

FAN.CNT 3

|    | PATENT NO. | KIND | DATE     | APPLICATION NO. | DATE         |
|----|------------|------|----------|-----------------|--------------|
| PI | US 5884230 | A    | 19990316 | US 1996-663809  | 19960614 <-- |

US 5453937 A 19950926 US 1993-55050 19930428 <--  
 US 5557535 A 19960917 US 1994-234812 19940428 <--  
 PRAI US 1993-55050 19930428 <--  
 US 1994-234812 19940428 <--

AB A method in a **computer** system for **modeling** a three-dimensional **structure** of a **model protein** is provided. In one embodiment, the **modeling** is based upon a three-dimensional **structure** of a template **protein** and an **amino acid** sequence alignment of the **model protein** and the template **protein**. For each **amino acid** in the **model protein**, when the template **protein** has an **amino acid** aligned with the **amino acid** of the **model protein**, the position of the backbone atom of the **amino acid** of the **model protein** is established based on the position of a topol. equiv. backbone atom in the aligned **amino acid** of the template **protein**. In another embodiment, the **modeling** of a variable region of the **model protein** is based on a collection of .psi. and .phi. **angle** values for **amino acid** pairs in a family of **proteins**. In a further embodiment, these .psi. and .phi. **angle** values are classified according to a tetramer of adjacent **amino acids** and filtered based on a most probable **conformation** of portions of the variable region of the **model protein**.

ST **protein** three dimensional **structure modeling**

IT **Algorithm**

**Simulation and Modeling**, physicochemical  
 (method and system for **protein modeling**)

IT **Amino acids**, properties

**Proteins**, general, properties

RL: PRP (Properties)

(method and system for **protein modeling**)

IT **Conformation**

(**protein**; method and system for **protein modeling**)

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L86 ANSWER 10 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1999:83909 HCAPLUS

DN 130:237856

- TI **Density** functional calculation of the electronic **structure** for **peptide-ligand** interactions
- AU Bohr, H.; Jalkanen, Karl
- CS Institute of Physics, b.307, The Technical University of Denmark, Lyngby, 2800, Den.
- SO Condensed Matter Theories (1998), 13, 95-112  
CODEN: CMTHEO; ISSN: 0893-861X
- PB Nova Science Publishers, Inc.
- DT Journal
- LA English
- CC 34-3 (Amino Acids, Peptides, and Proteins)  
Section cross-reference(s): 22
- AB Quantum mech. calcs. of the electronic **structure** of di- and **tripeptides** in aq. soln. were carried out using d. functional techniques. The **conformational** energies, bond lengths, dihedral angles, and spectroscopical properties of zwitterionic **structures** stabilized by different amts. of H<sub>2</sub>O **mols.** were listed for L-alanyl-L-alanine. The stable zwitterionic **structures** given here were quite different from those reported by Barron et al. (1991). The usefulness of neural networks for the prediction of **secondary structures** was demonstrated for N-acetyl-L-alanine N'-methylamide.
- ST **peptide** aq soln electronic **structure density** functional theory; **conformational** energy **peptide** aq soln DFT
- IT **Conformational** potential  
**Density** functional theory  
Electronic **structure**  
(electronic **structure** and **conformational** energy of di- and **tripeptides** in aq. soln. calcd. by d. functional techniques)
- IT **Peptides**, properties  
RL: PRP (Properties)  
(electronic **structure** and **conformational** energy of di- and **tripeptides** in aq. soln. calcd. by d. functional techniques)
- IT **Simulation and Modeling, physicochemical**  
(neural network; electronic **structure** of di- and **tripeptides** in aq. soln. calcd. by d. functional techniques using neural networks)
- IT Circular dichroism  
**Molecular structure**  
Vibrational spectra  
(of di- and **tripeptides** in aq. soln. calcd. by d. functional techniques)
- IT 56-41-7, L-Alanine, properties 1948-31-8 19701-83-8,  
N-Acetyl-L-alanine N'-methylamide  
RL: PRP (Properties)  
(electronic **structure** and **conformational** energy of di- and **tripeptides** in aq. soln. calcd. by d. functional techniques)
- RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L86 ANSWER 11 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1998:576388 HCAPLUS

DN 129:287073

TI Dictionary of interfaces in **proteins** (DIP). Data bank of complementary **molecular surface patches**

AU **Peissner, Robert; Goede, Andrean; Frommel, Cornelius**

CS Institute of Biochemistry, Medical Faculty of the Humboldt University (Charite), Berlin, D-10117, Germany

SO Journal of Molecular Biology (1998), 280(3), 535-550  
CODEN: JMOBAK; ISSN: 0022-2836

PB Academic Press

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB **Mol. surface areas of proteins** are responsible for selective **binding of ligands** and **protein-protein recognition**, and are considered the basis for specific interactions between different parts of a **protein**. This basic principle leads us to study the interfaces within **proteins** as a learning set for intermol. **recognition** processes of **ligands** like substrates, coenzymes, etc., and for prediction of contacts occurring during **protein folding** and assocn. For this purpose, we defined interfaces as pairs of matching **mol. surface patches** between neighboring **secondary structural** elements. All such interfaces from known **protein structures** were collected in a comprehensive data bank of interfaces in **proteins** (DIP). The up-to-date DIP contains interface files for 351 selected Brookhaven **Protein Data Bank** entries with a total of about 160,000 **surface** elements formed by 12,475 **secondary structures**. For special purposes, the inclusion of addnl. **structures** or selection of subgroups of **proteins** can be performed in an easy and straightforward manner. At. **coordinates** of the constituents of **mol. surface patches** are directly accessible as well as the corresponding contact distances from given atoms to their neighboring **secondary structural** elements. As a rule, independent of the type of **secondary structure**, the **mol. surface patches** of the **secondary structural** elements can be described as quite flat bodies with a length to width to depth ratio of about 3:2:1 for **patches** consisting of more than ten atoms. The relative orientation between two docking **patches** is strongly restricted, due to the narrow distribution of the distances between their centers of mass and of the **angles** between their normal lines, resp. The existing retrieval system for the DIP allows selection (out of the set of **mol. patches**) according to different criteria, such as geometric features, at. compn., type of **secondary structure**, contacts, etc. A fast, sequence-independent 3-D superposition procedure was developed for automatic searches for geometrically similar **surface areas**. Using this procedure, we found a large no. of **structurally** similar interfaces of up to 30 atoms in completely unrelated **protein structures**. (c) 1998 Academic Press.

ST **protein DIP database folding**

**conformation docking**

IT **Databases**

**Protein folding**

(dictionary of interfaces in **proteins** (DIP))

IT **Proteins, general, properties**

RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)

(dictionary of interfaces in **proteins** (DIP))

IT **Conformation**

(**protein**; dictionary of interfaces in **proteins** (DIP))

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L86 ANSWER 12 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1998:534531 HCAPLUS

DN 129:227227

TI Flexible docking allowing induced fit in **proteins**: insights from an open to closed **conformational** isomers

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CS Department of Applied Mathematics and Computer Science, Weizmann Institute of Science, Rehovot, Israel

SO Proteins: Structure, Function, and Genetics (1998), 32(2), 159-174

CODEN: PSFGEY; ISSN: 0887-3585

PB Wiley-Liss, Inc.

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB Here we dock a **ligand** onto a receptor **surface** allowing hinge-bending domain/substructural movements. Our approach mimics and manifests induced fit in **mol. recognition**. All **angular** rotations are allowed on the one hand, while a **conformational** space search is avoided on the other. Rather than dock each of the **mol.** parts sep. with subsequent reconstruction of the consistently docked **mols.**, all parts are docked simultaneously while still utilizing the position of the hinge from the start. Like pliers closing on a screw, the receptor automatically closes on its **ligand** in the best **surface**-matching way. Movements are allowed either in the **ligand** or in the larger receptor, hence reproducing induced **mol.** fit. Hinge bending

movements are frequently obsd. when **mols.** assoc. There are numerous examples of open vs. closed **conformations** taking place upon **binding**. Such movements are obsd. when the substrate **binds** to its resp. **enzyme**. In particular, such movements are of interest in allosteric **enzymes**. The movements can involve entire domains, subdomains, loops, (other) **secondary structure** elements, or between any groups of atoms connected by flexible joints. We have implemented the hinges at points and at bonds. By allowing 3-dimensional (**3-D**) rotation at the hinge, several rotations about (consecutive or nearby) bonds are implicitly taken into account. Alternatively, if required, the point rotation can be restricted to bond rotation. Here we illustrate this hinge-bending docking approach and the insight into flexibility it provides on a complex of the calmodulin with its M13 **ligand**, positioning the hinges either in the **ligand** or in the larger receptor. This automated and efficient method is adapted from **computer vision** and **robotics**. It enables utilizing entire **mol. surfaces** rather than focusing a priori on active sites. Hence, allows attaining the overall optimally matching **surfaces**, the extent and type of motions which are involved. Here we do not treat the **conformational** flexibility of side-chains or of very small pieces of the **mols**. Therefore, currently available methods addressing these issues and the method presented here, are complementary to each other, expanding the repertoire of **computational** docking tools foreseen to aid in studies of **recognition**, **conformational** flexibility and drug **design**.

ST calmodulins receptor **mol conformation** rotation  
**recognition**

IT **Molecular recognition**

**Molecular** rotation

(flexible docking allowing induced fit in **proteins**: insights from an open to closed **conformational** isomers)

IT Calmodulins

Receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(flexible docking allowing induced fit in **proteins**: insights from an open to closed **conformational** isomers)

IT **Conformation**

(**protein**; flexible docking allowing induced fit in **proteins**: insights from an open to closed **conformational** isomers)

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L86 ANSWER 13 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:802613 HCAPLUS

DN 128:137767

TI Mode matches and their locations in the hydrophobic free energy sequences  
of **peptide ligands** and their receptor eigenfunctions

AU Mandell, Arnold J.; Selz, Karen A.; Shlesinger, Michael F.

CS Cielo Inst., Asheville, NC, 28804, USA

SO Proceedings of the National Academy of Sciences of the United States of  
America (1997), 94(25), 13576-13581

CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal  
 LA English  
 CC 6-3 (General Biochemistry)  
 AB Patterns in sequences of **amino acid** hydrophobic free energies predict **secondary structures** in **proteins**. In **protein folding**, matches in hydrophobic free energy statistical wavelengths appear to contribute to selective aggregation of **secondary structures** in "hydrophobic zippers.". In a similar setting, the use of Fourier anal. to characterize the dominant statistical wavelengths of **peptide ligands'** and receptor **proteins'** hydrophobic modes to predict such matches has been limited by the aliasing and end effects of short **peptide** lengths, as well as the broad-band, mode multiplicity of many of their frequency (power) spectra. In addn., the sequence locations of the matching modes are lost in this transformation. We make new use of three techniques to address these difficulties: (i) eigenfunction construction from the linear decompn. of the lagged covariance matrixes of the **ligands** and receptors as hydrophobic free energy sequences; (ii) max. entropy, complex poles power spectra, which select the dominant modes of the hydrophobic free energy sequences or their eigenfunctions; and (iii) discrete, best bases, trigonometric wavelet transformations, which confirm the dominant spectral frequencies of the eigenfunctions and locate them as (abs. valued) moduli in the **peptide** or receptor sequence. The leading eigenfunction of the covariance matrix of a transmembrane receptor sequence locates the same transmembrane segments seen in n-block-averaged hydropathy plots while leaving the remaining hydrophobic modes unsmoothed and available for further analyses as **secondary** eigenfunctions. In these receptor eigenfunctions, we find a set of statistical wavelength matches between **peptide ligands** and their G-protein and tyrosine kinase coupled receptors, ranging across examples from 13.10 **amino acids** in acid fibroblast growth factor to 2.18 residues in corticotropin releasing factor. We find that the wavelet-located receptor modes in the extracellular loops are compatible with studies of receptor chimeric exchanges and point mutations. A nonbinding corticotropin-releasing factor receptor mutant is shown to have lost the signatory mode common to the normal receptor and its **ligand**. Hydrophobic free energy eigenfunctions and their transformations offer new quant. phys. homologies in **database** searches for **peptide-receptor** matches.

ST receptor **peptide ligand binding** hydrophobic  
 zippering; **amino acid** hydrophobicity free energy  
**binding**

IT Free energy  
 (hydrophobic, of **amino acids**; mode matches and  
 their locations in hydrophobic free energy sequences of **peptide**  
**ligands** and their receptor eigenfunctions)

IT **Amino acids**, biological studies  
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP  
 (Properties); BIOL (Biological study); PROC (Process)  
 (hydrophobic; mode matches and their locations in hydrophobic free  
 energy sequences of **peptide ligands** and their  
 receptor eigenfunctions)

IT Entropy  
 Hydrophobic force  
**Molecular association**  
**Molecular modeling**  
 (mode matches and their locations in hydrophobic free energy sequences  
 of **peptide ligands** and their receptor  
 eigenfunctions)

IT G **protein-coupled receptors**  
**Ligands**  
**Peptides**, biological studies

## Receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
 (mode matches and their locations in hydrophobic free energy sequences of **peptide ligands** and their receptor eigenfunctions)

IT **Protein motifs**

(transmembrane segment; mode matches and their locations in hydrophobic free energy sequences of **peptide ligands** and their receptor eigenfunctions)

## IT Receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
 (tyrosine kinase-coupled; mode matches and their locations in hydrophobic free energy sequences of **peptide ligands** and their receptor eigenfunctions)

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L86 ANSWER 14 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:801238 HCAPLUS

DN 128:164152

TI De novo heme **proteins** from **designed** combinatorial libraries

AU Rojas, Nina R. L.; Kamtekar, Satwik; Simons, Cyrena T.; Mclean, Jeremy E.; Vogel, Kathleen M.; Spiro, Thomas G.; Farid, Ramy S.; Hecht, Michael H.

CS Department of Chemistry, Princeton University, Princeton, NJ, 08544, USA

SO Protein Science (1997), 6(12), 2512-2524

CODEN: PRCIEI; ISSN: 0961-8368

PB Cambridge University Press

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB The authors previously reported the **design** of a library of de novo **amino acid** sequences targeted to **fold** into four-helix bundles. The **design** of these sequences was based on a "binary code" strategy, in which the patterning of polar and nonpolar **amino acids** is specified explicitly, but the exact identities of the side chains is varied extensively (Kamtekar S, Schiffer JM, Xiong H, Babik JM, Hecht MH, 1993, Science 262: 1680-1685). Because of this variability, the resulting collection of **amino acid** sequences may include de novo **proteins** capable of **binding** biol. important cofactors. To probe for such **binding**, the de novo sequences were **screened** for their ability to **bind** the heme cofactor. Among an initial collection of 30 binary code sequences, 15 are shown to **bind** heme and form bright red complexes. Characterization of several of these de novo heme **proteins** demonstrated that their absorption spectra and resonance Raman spectra resemble those of natural cytochromes. Because the **design** of these sequences is based on global features of polar/nonpolar patterning, the finding that half of them **bind** heme highlights the power of the binary code strategy, and demonstrates that isolating de novo heme **proteins** does not require explicit



**design** of the cofactor **binding** site. Because bound heme plays a key role in the functions of many natural **proteins**, these results suggest that binary code sequences may serve as initial prototypes for the development of large collections of functionally active de novo **proteins**.

ST heme **protein design** combinatorial library

IT Absorption spectra

Combinatorial library

Dissociation constant

**Molecular association**

**Molecular modeling**

**Peptide** library

**Protein** engineering

**Protein** sequences

Resonance Raman spectra

Thermal stability

(characterization of heme-**binding proteins** from **designed** combinatorial libraries)

IT Cytochromes

**Hemoproteins**

RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process)

(characterization of heme-**binding proteins** from **designed** combinatorial libraries)

IT **Structure-activity** relationship

(**ligand-binding**, heme-**binding**;

characterization of heme-**binding proteins** from **designed** combinatorial libraries)

IT **Secondary structure**

(**protein**; characterization of heme-**binding**

**proteins** from **designed** combinatorial libraries)

IT 153224-44-3P 153224-45-4P 153224-46-5P 202759-01-1P 202759-02-2P

202759-03-3P 202759-04-4P 202759-05-5P 202759-06-6P 202759-07-7P

202759-08-8P 202759-09-9P 202759-10-2P 202759-11-3P 202759-12-4P

202759-13-5P 202759-14-6P 202759-15-7P 202759-16-8P 202759-17-9P

202759-18-0P 202759-19-1P 202759-20-4P 202759-21-5P 202759-22-6P

202759-23-7P 202759-24-8P 202759-25-9P 202759-26-0P 202759-27-1P

RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process)

(**amino acid** sequence; characterization of heme-**binding proteins** from **designed** combinatorial libraries)

IT 493-90-3, Mesoporphyrin IX 14875-96-8, Heme

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(characterization of heme-**binding proteins** from **designed** combinatorial libraries)

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L86 ANSWER 15 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:638464 HCAPLUS

DN 127:314402

TI Constrained Corticotropin-Releasing Factor Antagonists with i-(i + 3) Glu-Lys Bridges

AU Miranda, Antonio; Lahrichi, Sabine L.; Gulyas, Jozsef; Koerber, Steven C.; Craig, Anthony G.; Corrigan, Anne; Rivier, Catherine; Vale, Wylie; Rivier, Jean

CS Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, CA, 92037, USA

SO Journal of Medicinal Chemistry (1997), 40(22), 3651-3658  
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

CC 1-3 (Pharmacology)

Section cross-reference(s): 2, 34

AB Hypothesis driven and systematic **structure**-activity relationship (SAR) investigations have resulted in the development of effective central nervous system (CNS) antagonists of corticotropin (ACTH)-releasing factor (CRF) such as .alpha.-helical CRF(9-41) and analogs of our assay std. [DPhel2,Nle21,38]hCRF(12-41). On the other hand, equally potent CRF antagonists that block the hypothalamic/pituitary/adrenal (HPA) **axis** had not been described until recently. Predictive methods, physicochem. measurements (NMR spectrometry and CD spectroscopy), and SAR studies suggest that CRF and its family members (urotensins and sauvagine) assume an .alpha.-helical **conformation** when interacting with CRF receptors. To further test this hypothesis, we have systematically scanned the hCRF(9-41) or hCRF(12-41) sequences with an i-(i + 3) bridge consisting of the Glu-Xaa-Xbb-Lys scaffold which we and others had shown

could maintain or enhance .alpha.-helical **structure**. From this series we have identified seven analogs that are either equipotent to, or 3 times more potent than, the assay std.; in addn., as presented earlier, cyclo(30-33)[DPhe12,Nle21,38,Glu30,Lys33]hCRF(12-41) (astressin) is 32 times more potent than the assay std. in blocking ACTH secretion in vitro (rat pituitary cell culture assay). In vivo, astressin is also significantly more potent than earlier antagonists at reducing hypophyseal ACTH secretion in intact stressed or adrenalectomized rats. Since the corresponding linear analogs that were tested are significantly less potent, our interpretation of the increased potency of the cyclic analogs is that the introduction of the side chain to side chain bridging element (Glu30---Lys33, and to a lesser extent that of Glu14---Lys17, Glu20---Lys23, Glu23---Lys26, Glu26---Lys29, Glu28---Lys31, Glu29---Lys32, and Glu33---Lys36) induces and stabilizes in the receptor environment a putative .alpha.-helical bioactive **conformation** of the fragment that is not otherwise heavily represented. The effect of the introduction of two favored substitutions [cyclo(20-23) and cyclo(30-33)] yielded the compd. with a potency 8 times that of the assay std. but actually 12 times less than expected if the effect of the two cycles had been multiplicative. These results suggest that the pituitary CRF receptor can discriminate between slightly different identifiable **conformations**, dramatically illustrating the role that **secondary** and tertiary **structures** play in modulating biol. signaling through specific **protein-ligand** interactions.

- ST corticotropin releasing factor antagonist prepn **structure**; CRF receptor antagonist signaling **ligand structure**
- IT Pituitary gland
  - (CRF receptors of; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT Endocrine system
  - (adrenal-hypothalamus-pituitary, blocking of, CRF antagonists for; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT Nervous system
  - (central; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT Corticotropin releasing factor receptors
  - RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
  - (interactions with; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT Signal transduction, biological
  - (modulation of; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT **.alpha.-Helix**
  - (prepn. and **structure** of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT **Ligands**
  - RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
  - (prepn. and **structure** of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT **Molecular modeling**
  - (prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT **Structure-activity relationship**
  - (receptor-inhibiting; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
- IT 9015-71-8, Corticotropin-releasing factor
  - RL: BSU (Biological study, unclassified); BIOL (Biological study)
  - (analogs; prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)

IT 129133-27-3P 158068-34-9P 158068-54-3P 170809-51-5P 170809-52-6P  
 183615-11-4P 183615-13-6P 183615-16-9P 183615-18-1P 183615-20-5P  
 183615-23-8P 183615-25-0P 183615-27-2P 183615-28-3P 183868-57-7P  
 183906-02-7P 197443-72-4P 197443-73-5P 197443-74-6P 197443-75-7P  
 197443-76-8P 197443-77-9P 197443-78-0P 197443-79-1P 197443-80-4P  
 197443-81-5P 197443-82-6P 197443-83-7P 197443-84-8P 197443-85-9P  
 197443-86-0P 197527-39-2P 197527-40-5P 197527-41-6P 197527-42-7P  
 197527-43-8P 197527-44-9P 197527-45-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)

(prepn. of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)

L86 ANSWER 16 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1997:499201 HCAPLUS

DN 127:157214

TI **Computer-assisted design** of morphogen analogs from the atomic x-ray crystallographic **coordinates** of human osteogenic **protein** OP-1

IN Keck, Peter; Griffith, Diana L.; Carlson, William D.; Rueger, David C.; Sampath, Kuber T.

PA Creative Biomolecules, Inc., USA; Brandeis University

SO PCT Int. Appl., 176 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07K014-51

ICS G06F017-50

CC 2-2 (Mammalian Hormones)

FAN.CNT 2

|      | PATENT NO.  | KIND | DATE     | APPLICATION NO. | DATE         |
|------|---|------|----------|-----------------|--------------|
| PI   | WO 9726277  | A2   | 19970724 | WO 1997-US1071  | 19970122 <-- |
|      | W: AU, CA, JP   |      |          |                 |              |
|      | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE    |      |          |                 |              |
|      | CA 2244228  | AA   | 19970724 | CA 1997-2244228 | 19970122 <-- |
|      | AU 9722449  | A1   | 19970811 | AU 1997-22449   | 19970122 <-- |
|      | AU 725295   | B2   | 20001012 |                 |              |
|      | EP 876401   | A2   | 19981111 | EP 1997-905604  | 19970122 <-- |
|      | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI |      |          |                 |              |
|      | JP 2000501744   | T2   | 20000215 | JP 1997-526303  | 19970122 <-- |
| PRAI | US 1996-589552  | A    | 19960122 | <--             |              |
|      | WO 1997-US1071  | W    | 19970122 | <--             |              |

AB Methods and compns. are provided for the **computer-assisted design** of morphogen analogs. Practice of the invention is enabled by the use of at least a portion of the at. **coordinates** defining the 3-dimensional **structure** of human osteogenic **protein** -1 (hOP-1) as a starting point in the **design** of the morphogen analogs. In addn., the invention provides methods for producing morphogen analogs of interest, and methods for testing whether the resulting analogs mimic or agonize human OP-1-like biol. activity. A family of morphogen analog **peptides** produced by such methods is also provided.

ST morphogen **design** osteogenic **protein** crystal **structure**

IT Bone morphogenetic **proteins**

RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)

(7; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein** OP-1)

- IT **Computer application**  
**Crystal structure**  
**Drug design**  
**Molecular modeling**  
(**computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT **Proteins, specific or class**  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(morphogenetic; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT **Protein sequences**  
(of morphogen analogs **designed** from human osteogenic **protein OP-1**)
- IT **Conformation**  
(**protein; computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT 193465-55-3P 193465-56-4P 193465-57-5P 193465-58-6P 193465-59-7P  
193465-60-OP 193562-94-6P  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(**computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT 193562-95-7P  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(dimer stabilization; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT 193562-96-8P  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(enhanced water soly.; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT 193562-51-5P  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(finger 1 region of OP-1; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT 193562-49-1P  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(finger 2 region of OP-1; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates** of human osteogenic **protein OP-1**)
- IT 193562-50-4P  
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(heel region of OP-1; **computer-assisted design** of morphogen analogs from the at. x-ray crystallog. **coordinates**)

of human osteogenic **protein** OP-1)

- L86 ANSWER 17 OF 26 HCAPLUS COPYRIGHT 2003 ACS  
AN 1997:446520 HCAPLUS  
DN 127:158732  
TI Voronoi cell: new method for allocation of space among atoms: elimination of avoidable errors in calculation of atomic volume and **density**  
AU **Goede, A.; Preissner, R.; Froemmel, C.**  
CS Institute of Biochemistry, Humboldt University, Berlin, D-10117, Germany  
SO Journal of Computational Chemistry (1997), 18(9), 1113-1123  
CODEN: JCCHDD; ISSN: 0192-8651  
PB Wiley  
DT Journal  
LA English  
CC 9-16 (Biochemical Methods)  
Section cross-reference(s): 6  
AB In **computing** the vol. occupied by atoms and the d. in **proteins**, one is faced with the problem of intersecting spheres. To est. either, the space between the atoms has to be divided according to the location of the atoms relative to each other. Various methods, based on Voronoi's idea of approximating the at. space by polyhedra, have been proposed for this purpose. Comparing procedures concerned with the allocation of space among distinct atoms, we observe different partitionings of space, with deviations of more than 100% for particular atoms. Furthermore, we find that the sepg. planes of different Voronoi procedures do not meet the intersection circles of covalently linked atoms. This leads to a misallocation of space of up to 7% for atom pairs that largely differ in at. size (e.g., C-H). Several **algorithms** are neg. affected by small unallocated polyhedra ("vertex error"). These effects are cumulative for a small **protein** up to a loss of some 60 .ANG.3 of total vol., which would correspond to the deletion of one complete residue. To overcome these errors, instead of using dividing planes between the atoms, we use curved **surfaces**, defined as the set of those geometrical loci with equal orthogonal distance to the **surfaces** of the van der Waals spheres under consideration. The proposed dividing **surface** meets not only the intersection circle of the two van der Waals spheres but also the intersection circle of the two spheres enlarged by an arbitrary value (e.g., radius of water). This hyperbolic **surface** enveloping the Voronoi cell can be easily constructed and offers the following advantages: no misallocation of vol. for atoms of different size, no vertex error, geometrically reasonable allocation of the vol. among atoms, avoidance of discontinuities between neighboring atoms, and improved applicability to water-accessible **protein surfaces**.  
ST Voronoi cell space atom calcn; atomic vol **density**  
IT Volume  
RL: ANT (Analyte); ANST (Analytical study)  
(at.; new method for allocation of space among atoms)  
IT **Algorithm**  
**Density**  
(new method for allocation of space among atoms)  
IT Atoms  
RL: ANT (Analyte); ANST (Analytical study)  
(new method for allocation of space among atoms)  
IT **Proteins**, general, properties  
RL: PRP (Properties)  
(new method for allocation of space among atoms)  
  
L86 ANSWER 18 OF 26 HCAPLUS COPYRIGHT 2003 ACS  
AN 1996:590946 HCAPLUS  
DN 125:269873  
TI Method and system for **protein modeling**

IN Srinivasan, Subhashini; Sudarsanam, Padmanaban  
 PA Immunex Corporation, USA  
 SO U.S., 21 pp., Cont.-in-part of U.S. 5, 453, 397.  
 CODEN: USXXAM  
 DT Patent  
 LA English  
 IC ICM G01N037-00  
 NCL 364496000  
 CC 9-16 (Biochemical Methods)  
 FAN.CNT 3

|      | PATENT NO.     | KIND | DATE         | APPLICATION NO. | DATE         |
|------|----------------|------|--------------|-----------------|--------------|
| PI   | US 5557535     | A    | 19960917     | US 1994-234812  | 19940428 <-- |
|      | US 5453937     | A    | 19950926     | US 1993-55050   | 19930428 <-- |
|      | US 5884230     | A    | 19990316     | US 1996-663809  | 19960614 <-- |
| PRAI | US 1993-55050  |      | 19930428 <-- |                 |              |
|      | US 1994-234812 |      | 19940428 <-- |                 |              |

AB A method in a **computer** system for **modeling** a three-dimensional **structure** of a **model protein** is provided. In a preferred embodiment, the **modeling** is based upon a three-dimensional **structure** of a template **protein** and an **amino acid** sequence alignment of the **model protein** and the template **protein**. The **proteins** comprise a plurality of **amino acids** having backbone atoms and side chain atoms. For each **amino acid** in the **model protein**, when the template **protein** has an **amino acid** aligned with the **amino acid** of the **model protein**, the position of each backbone atom of the **amino acid** of the **model protein** is established based on the position of a topol. equiv. backbone atom in the aligned **amino acid** of the template **protein**. The inter-at. distance constraints for each pair of atoms with an established position is generated. Finally, the position of each atom in the **model protein** is set so that the inter-at. distances are in accordance with the constraints.

ST system **protein model**

IT **Conformation and Conformers**

**Simulation and Modeling**, physicochemical  
 (method and system for **protein modeling**)

IT **Proteins**, properties

RL: PRP (Properties)

(method and system for **protein modeling**)

L86 ANSWER 19 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1996:104717 HCAPLUS

DN 124:197693

TI The automatic search for **ligand binding** sites in **proteins** of known three-dimensional **structure** using only geometric criteria

AU Peters, Klaus P.; Fauck, Jana; **Froemmel, Cornelius**

CS Inst. Biochem., Humboldt-Univ. Berlin, Berlin, D-10115, Germany

SO Journal of Molecular Biology (1996), 256(1), 201-13

CODEN: JMOBAK; ISSN: 0022-2836

PB Academic

DT Journal

LA English

CC 9-16 (Biochemical Methods)

Section cross-reference(s): 6

AB The biol. function of a **protein** typically depends on the **structure** of specific **binding** sites. These sites are located at the **surface** of the **protein mol.**

and are detd. by geometrical arrangements and physico-chem. properties of

tens of non-hydrogen atoms. In this paper we describe a new **algorithm** called APROPOS, based purely on geometric criteria for identifying such **binding** sites using at. **coordinates**. For the description of the **protein** shape we use an alpha-shape **algorithm** which generates a whole family of shapes with different levels of detail. Comparing shapes of different resolu. we find cavities on the **surface** of the **protein** responsible for **ligand binding**. The **algorithm** correctly locates more than 95% of all **binding** sites for **ligands** and prosthetic groups of **mol. mass** between about 100 and 2000 Da in a representative set of **proteins**. Only in very few **proteins** does the method find **binding** sites of single ions outside the active site of **enzymes**. With one exception, we observe that interfaces between subunits show different geometric features compared to **binding** sites of **ligands**. Our results clearly support the view that **protein-protein** interactions occur between flat areas of **protein surface** whereas specific interactions of smaller **ligands** take place in pockets in the **surface**.

ST **algorithm protein ligand binding**  
site searching

IT **Algorithm**  
(APROPOS; automatic search for **ligand binding** sites in **proteins** of known three-dimensional **structure** using only geometric criteria)

IT **Proteins, analysis**  
RL: ANT (Analyte); ANST (Analytical study)  
(automatic search for **ligand binding** sites in **proteins** of known three-dimensional **structure** using only geometric criteria)

IT **Conformation and Conformers**  
(three dimensional; automatic search for **ligand binding** sites in **proteins** of known three-dimensional **structure** using only geometric criteria)

IT **Proteins, specific or class**  
RL: ANT (Analyte); ANST (Analytical study)  
(FKBP (FK 506-**binding protein**), automatic search for **ligand binding** sites in **proteins** of known three-dimensional **structure** using only geometric criteria)

IT 9001-92-7, **Proteinase** 9014-01-1, Subtilisin 9024-82-2, Inorganic pyrophosphatase  
RL: ANT (Analyte); ANST (Analytical study)  
(automatic search for **ligand binding** sites in **proteins** of known three-dimensional **structure** using only geometric criteria)

L86 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1994:701318 HCAPLUS

DN 121:301318

TI Synthetic, stabilized, three-dimension **polypeptides**

IN Satterthwait, Arnold C., Jr.; Arrhenius, Thomas; Chiang, Lin Chang; Cabeza, Edelmina

PA Scripps Research Institute, USA

SO PCT Int. Appl., 132 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07K001-00

ICS C07K007-54; C07K015-00; A61K037-02; A61K039-00; A61K039-395; C12N015-00; G01N033-53

CC 34-3 (Amino Acids, Peptides, and Proteins)  
Section cross-reference(s): 1, 15



FAN.CNT 2

|      | PATENT NO.   | KIND | DATE     | APPLICATION NO. | DATE         |
|------|--|------|----------|-----------------|--------------|
| PI   | WO 9321206   | A1   | 19931028 | WO 1993-US3032  | 19930331 <-- |
|      | W: AU, CA, FI, JP, NO  |      |          |                 |              |
|      | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE |      |          |                 |              |
|      | AU 9339718   | A1   | 19931118 | AU 1993-39718   | 19930331 <-- |
|      | US 5807979   | A    | 19980915 | US 1995-456424  | 19950601 <-- |
| PRAI | US 1992-866040   |      | 19920408 |                 | <--          |
|      | US 1993-33883  |      | 19930319 |                 | <--          |
|      | US 1988-179160   |      | 19880408 |                 | <--          |
|      | US 1990-607645   |      | 19901029 |                 | <--          |
|      | US 1991-746064   |      | 19910812 |                 | <--          |
|      | WO 1993-US3032   |      | 19930331 |                 | <--          |
|      | US 1994-224059   |      | 19940407 |                 | <--          |
| OS   | CASREACT 121:301318  |      |          |                 |              |
| GI   |  |      |          |                 |              |

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB Synthesis of three-dimensional stabilized **peptides** which mimic the three-dimensional configuration of active site of a natural, biol. active **protein** is carried out by (1) noting the three-dimensional configuration of the active site of a known biol. active **protein**, (2) noting the **amino acid** sequence and the hydrogen bonds existing between **amino acids** and that hydrogen bonds are capable of maintaining the three-dimensional configuration of the active site, and (3) producing a synthetic three-dimensional **peptide** to mimic the **structure** of the active site. The synthetic **peptide** is synthesized so as to have the same or a similar **amino acid** sequence to the **amino acid** sequence of the active site of the biol. active **polypeptide** but with the stabilizing hydrogen bonds being replaced by a bridging divalent radical selected from the group consisting of aminomethane and aminoethane acetamidinium (N)CMe:N(H+)CH<sub>2</sub>(N), (N)CMe:N(H+)CH<sub>2</sub>CH<sub>2</sub>(N) (class I hydrogen bond mimics), and carboxybutanal hydrazone (N)N:CH(CH<sub>2</sub>)<sub>3</sub>(CO) (class II hydrogen bond mimic). Said **peptides** are represented by general cyclic **peptide** formulas (I; R<sub>1</sub>, R<sub>2</sub> = H, C1-6 alkyl; R<sub>3</sub> = H, C1-6 alkyl, chain of **amino acids** contg. 1-2,000 **amino acids**; aa = **amino acid**; n = 1-2,000; R<sub>4</sub> = any atom or mol. group of atoms with the required electron configuration; m = 0-6) and (II; R<sub>5</sub> = C1-6 alkoxy, PhO, naphthyloxy, benzoxy, NH<sub>2</sub>, an **amino acid** sequence contg. 1-2,000 **amino acids**; aa = **amino acid**; n = 1-2,000; m = integer, e.g. 2; X = optionally present and if present is selected from the group consisting of CH<sub>2</sub>, NH, :CH, and :NH with double bond to CHR; R<sub>6</sub> = optionally present and if present is selected from the group consisting of H, C1-6 alkyl, (CH<sub>2</sub>)<sub>1</sub>NH<sub>2</sub> (wherein 1 = 1-6) optionally connected to an **amino acid** chain contg. 1-2,000 **amino acids**]. The hydrogen bond mimic (class I) of the cyclic **peptide** I is formed by intramol. reaction of the thioimide group [generated by treating the corresponding thioamide R<sub>1</sub>C(S)NR<sub>2</sub>CHR<sub>3</sub>(CO) with MeI] of a **peptide** (III) with the primary NH<sub>2</sub> group. The cyclic **peptide** II are prepd. by intramol. cyclocondensation of the hydrazone group of a **peptide** (IV) with the di-Me acetal functional group, forming the other type of the hydrogen bond mimics (class II). Thus, 5 **conformationally** restricted HIV **peptides** with the hydrogen bond mimic (class II), e.g. cyclic **peptide** II [(aa)<sub>n</sub> = S-I-G-P-G-R-A-F-G, m = 2, X = bond, R<sub>6</sub> = H, R<sub>5</sub>

= Cys-NH<sub>2</sub>] (V), which is related to the V3 loop of the HIV gp120 **protein** identified as a neutralizing epitope, were prep'd. by the solid phase method. V bound to 3 HIV-**binding** murine monoclonal antibodies, at least one of which protected monkey against HIV, and reacted pos. using ELISA with sera from a patient with AIDS. HIV **peptide** II [(aa)<sub>n</sub> = S-I-S-I-G-P-G-R-A-F-Y-T-G, m = 2, X = bond, R = H, R = Cys-NH] was used to isolate human Fabs from combinatorial libraries by panning and these 5 **peptides** are potential synthetic vaccines for protection against AIDS. **Conformationally** restrained malaria **peptides** corresponding to neutralizing epitopes on various stages of *Plasmodium falciparum* malaria were also prep'd. and are useful as a multistage vaccine. Also prep'd. were epidermal growth factor analogs contg. carboxybutanal hydrazone linkage (class II) as hydrogen bond mimic.

ST three dimensional stabilized **peptide**; hydrogen bond mimic aminoethane acetamidinium; carboxybutanal hydrazone hydrogen bond mimic; malaria **peptide** neutralizing epitope; HIV gp120 **peptide** neutralizing epitope; human Fabs isolation panning HIV **peptide**; multistage vaccine malaria; vaccine HIV; **conformationally** restrained HIV malaria **peptide**; cyclic **peptide** **conformationally** restrained; active site **protein** hydrogen bond mimic; cyclization thioimide primary amine **peptide**; *Plasmodium falciparum* vaccine cyclic **peptide**; epidermal growth factor cyclic **peptide** analog

IT Antigens

RL: SPN (Synthetic preparation); PREP (Preparation)  
(HIV and malaria neutralizing epitope-related three-dimensional stabilized cyclic **peptides** having hydrogen bond mimics, prepn. of, for prodn. of vaccines against HIV and malaria)

IT Vaccines

(for HIV and malaria, HIV and malaria neutralizing epitope-related three-dimensional stabilized cyclic **peptides** having hydrogen bond mimics for prodn. of)

IT **Peptides**, preparation

RL: SPN (Synthetic preparation); PREP (Preparation)  
(hydrogen bond mimics (aminomethane or aminoethane acetamidinium or carboxybutanal hydrazone linkage), prepn. of, by cyclization of N-[N-(dimethoxy)butyrylpeptidyl]hydrazine derivs. or S-methylthioimides from (thioacetyl)**peptide** (aminoethyl)amides)

IT Ring closure and formation

(of N-[N-(dimethoxy)butyrylpeptidyl]hydrazine derivs. or S-methylthioimide deriv. from N-(thioacetyl)**peptide** -N-(aminoethyl or aminomethyl)amide, cyclic **peptides** contg. hydrazone hydrogen bond mimics)

IT *Plasmodium falciparum*

(vaccines for, cyclic **peptides** contg. hydrogen bond mimics as)

IT Malaria

(vaccines for, three-dimensional stabilized cyclic **peptides** having hydrogen bond mimics for)

IT **Peptides**, preparation

RL: SPN (Synthetic preparation); PREP (Preparation)  
(cyclo-, with hydrogen bond mimics (aminomethane or aminoethane acetamidinium or carboxybutanal hydrazone linkage), HIV or malaria neutralizing epitope-related, prepn. of, as vaccines against AIDS and malaria)

IT Sialoglycoproteins

RL: SPN (Synthetic preparation); PREP (Preparation)  
(gp120env, V3 loop of, three-dimensional stabilized cyclic **peptides** having hydrogen bond mimics related to, prepn. of, as antigens for prodn. of vaccines against HIV)

IT Virus, animal

- (human immunodeficiency 1, vaccines for, three-dimensional stabilized cyclic **peptides** having hydrogen bond mimics for)
- IT 26386-88-9, Diphenylphosphoryl azide  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acyl azide formation and Curtius rearrangement of, with alanylglycine deriv.)
- IT 501-53-1, Benzyloxycarbonyl chloride  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acylation by, of ethylenediamine)
- IT 24424-99-5, Di-tert-butyl dicarbonate 28920-43-6, 9-Fluorenylmethyloxycarbonyl chloride  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acylation by, of ethylenediamine deriv.)
- IT 1738-69-8, Leucine benzyl ester  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acylation of, by (dimethoxy)pentanoic acid)
- IT 107-15-3, 1,2-Ethanediamine, reactions  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acylation of, by benzyloxycarbonyl chloride)
- IT 14794-31-1, Ethyl succinyl chloride  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acylation of, by ethylenediamine deriv.)
- IT 159002-17-2  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(acylation of, by fluorenylmethyloxycarbonyl chloride)
- IT 75-65-0, tert-Butyl alcohol, reactions  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(addn. of, with alanylaminomethyl isocyanate deriv.)
- IT 33294-53-0  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(condensation of, with Et N-aminoglycinate deriv.)
- IT 67-64-1, Acetone, reactions  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(condensation of, with Et hydrazinoacetate)
- IT 6945-92-2, Ethyl hydrazinoacetate hydrochloride  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(condensation of, with acetone)
- IT 35661-39-3, Fmoc-Ala-OH  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(condensation of, with resin-bound aminoalanine deriv.)
- IT 1142-20-7, Z-Ala-OH  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(esterification of, with N-hydroxysuccinimide)
- IT 6066-82-6, N-Hydroxysuccinimide  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(esterification of, with alanine deriv.)
- IT 107-97-1, Sarcosine  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(esterification of, with benzyl alc.)
- IT 100-51-6, Benzyl alcohol, reactions  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(esterification of, with sarcosine)
- IT 123639-61-2, Fmoc-Glu(OBzl)-OH  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(esterification with methanol, hydrogenolysis, and chlorination with thionyl chloride)
- IT 159002-15-0  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(hydrogenolysis and acylation of, by fluorenylmethyloxycarbonyl chloride)
- IT 74-88-4, Methyl iodide, reactions  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(methylation by, of N-(thioacetyl)**peptide**, S-thioimide)

deriv. from)

IT 56-40-6, Glycine, reactions  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(**peptide** coupling of, with alanine deriv.)

IT 2304-94-1, N-(Benzyloxycarbonyl)-.beta.-alanine  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(**peptide** coupling of, with glycine deriv.)

IT 1738-68-7, Benzyl glycinate  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(**peptide** coupling of, with .beta.-alanine deriv.)

IT 126166-23-2P 126166-24-3P 126166-25-4P 157411-67-1P 158965-98-1P  
158966-00-8P 158966-19-9P 158966-26-8P 158966-27-9P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(prepn. and cyclization of)

IT 158965-97-0P  
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT  
(Reactant or reagent)  
(prepn. and cyclization of, cyclic **peptide** with hydrogen bond  
mimic from)

IT 637-80-9P, Ethyl hydrazinoacetate 54384-05-3P, Sarcosine benzyl ester  
122652-52-2P 158966-06-4P 158966-07-5P 159002-12-7P 159002-13-8P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of)

IT 158966-32-6P 158966-33-7P 158966-34-8P 158966-35-9P 158966-36-0P  
158966-37-1P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as HIV gp120 **protein**-neutralizing epitope mimic  
for prodn. of HIV vaccine)

IT 158966-17-7P 158966-18-8P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as antigen for prodn. of malaria vaccine)

IT 158966-01-9P 158966-02-0P 159002-14-9P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as epidermal growth factor analog contg. carboxybutanal  
hydrazone linkage as hydrogen bond mimic)

IT 130851-23-9DP, leucine-modified resin-bound 130851-23-9P  
159002-16-1DP, leucine-modified resin-bound 159002-16-1P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as intermediate for cyclic **peptide** contg.  
acetamidinium linkage as hydrogen bond mimic)

IT 57260-73-8P, N-(tert-Butoxycarbonyl)ethylenediamine 72080-83-2P,  
N-(Benzyloxycarbonyl)ethylenediamine 77153-05-0P, N-(Benzyloxycarbonyl)-  
N'-(tert-butoxycarbonyl)ethylenediamine 126166-08-3P 126166-09-4P  
126166-10-7P 126166-11-8P 126166-12-9P 126166-13-0P 126198-37-6P,  
N-Thioacetylsarcosine  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as intermediate for cyclic **peptide** contg.  
aminoethane acetamidinium linkage as hydrogen bond mimic)

IT 158966-08-6P 158966-09-7P 158966-10-0DP, resin bound 158966-10-0P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as intermediate for cyclic **peptide** contg.  
aminoethane amidinium linkage as hydrogen bond mimic)

IT 3235-17-4P, Z-Ala-Gly-OH 3401-36-3P, Z-Ala-OSu 126166-00-5P  
126166-01-6P 126166-02-7P 126166-04-9P, Benzyl N-acetylsarcosinate  
126166-05-0P, Benzyl N-(thioacetyl)sarcosinate 126166-06-1P  
126166-07-2P 126198-36-5P 126198-37-6P, N-(Thioacetyl)sarcosine  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, as intermediate for cyclic **peptide** contg.  
aminomethane acetamidinium linkage as hydrogen bond mimic)

IT 6719-33-1P, 5,5-(Dimethoxy)pentanoic acid 126166-16-3P 126166-17-4P  
126166-19-6P 126166-20-9P 126166-21-0P 126166-22-1P 158965-99-2P,  
Ethyl N-(isopropylidene)hydrazinoacetate hydrochloride 158966-03-1DP,

resin-bound 158966-03-1P 158966-11-1P 158966-12-2DP, Rink amide  
 resin 158966-13-3P 158966-14-4P 158966-15-5P 158966-16-6P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of, as intermediate for cyclic **peptide** contg.  
 carboxybutanal hydrazone linkage as hydrogen bond mimic)  
 IT 30593-19-2P, Benzyl N-(benzyloxycarbonyl)-.beta.-alanylglycinate  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of, as intermediate for cyclic **peptide** contg.  
 hydrogen bond mimic)  
 IT 158966-28-0P 158966-29-1P 158966-30-4P 158966-31-5P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of, as merozoite **surface protein-1** epitope  
 mimic for prodn. of malaria vaccine)  
 IT 158966-20-2P 158966-21-3P 158966-22-4P 158966-23-5P 158966-24-6P  
 158966-25-7P  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn. of, as pfs25 neutralizing epitope mimic for prodn. of malaria  
 vaccine)  
 IT 158966-04-2DP, leucine-modified resin-bound 158966-05-3DP,  
 leucine-modified resin-bound  
 RL: SPN (Synthetic preparation); PREP (Preparation)  
 (prepn., methylation with Me iodide, deprotection and  
 resin-cleavage-cyclization of)  
 IT 23068-91-9, Methyl 5,5-(dimethoxy)pentanoate  
 RL: RCT (Reactant); RACT (Reactant or reagent)  
 (sapon. of)

L86 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2003 ACS  
 AN 1993:120490 HCAPLUS  
 DN 118:120490  
 TI A method to identify **protein** sequences that **fold** into  
 a known three-dimensional **structure**  
 IN Eisenberg, David; Bowie, James U.; Luthy, Roland  
 PA University of California, USA  
 SO PCT Int. Appl., 56 pp.  
 CODEN: PIXXD2

DT Patent  
 LA English  
 IC ICM G01N  
 CC 9-16 (Biochemical Methods)  
 Section cross-reference(s): 6, 20

FAN.CNT 1

|      | PATENT NO.   | KIND | DATE         | APPLICATION NO. | DATE         |
|------|--|------|--------------|-----------------|--------------|
| PI   | WO 9301484   | A2   | 19930121     | WO 1992-US5773  | 19920710 <-- |
|      | W: AU, CA, JP  |      |              |                 |              |
|      | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE |      |              |                 |              |
|      | AU 9224082   | A1   | 19930211     | AU 1992-24082   | 19920710 <-- |
|      | US 5436850   | A    | 19950725     | US 1994-218685  | 19940328 <-- |
| PRAI | US 1991-728640   |      | 19910711 <-- |                 |              |
|      | WO 1992-US5773   |      | 19920710 <-- |                 |              |

AB A **computer**-assisted method is disclosed for identification of  
**protein** sequences that **fold** into a known  
 three-dimensional (3D) **structure**. The method detcs. 3  
 key features of each residue's environment within the **structure**:  
 (1) the total area of the residue's side-chain that is buried by other  
**protein** atoms, inaccessible to solvent; (2) the fraction of the  
 side-chain area that is covered by polar atoms (O, N) or water; and (3)  
 the local **secondary structure**. Based on these  
 parameters, each residue position is categorized into an environment  
 class. In this manner, a **3D protein structure**  
 is converted into a 1D environment string. A **3D**  
**structure** profile table is then created contg. score values that

- represent the frequency of finding any of the 20 common **amino acid structures** at each position of the environment string. These frequencies are detd. from a **database** of known **protein structures** and aligned sequences. Included are 3D compatibility search examples using a 3D **structure** profile for e.g. myoglobin or cyclic AMP receptor **protein**.
- ST **protein** identification **computer** three dimensional **structure**; **conformation** **protein** **computer**
- IT Water of hydration  
(**amino acid** side-chain area fraction covered by, detn. of, in **computer**-assisted identification of **protein** with known three-dimensional **structure**)
- IT Solvents  
(**amino acid** side-chain area inaccessible to, detn. of, in **computer**-assisted identification of **protein** with known three-dimensional **structure**)
- IT **Proteins**, analysis  
RL: PRP (Properties)  
(**conformation** of, **computer**-assisted detn. of)
- IT **Computer** application  
(in identification of **protein** with known three-dimensional **structure**)
- IT **Conformation** and **Conformers**  
(of **proteins**, three-dimensional, **computer**-assisted detn. of)
- IT Atoms  
(polar, **amino acid** side-chain area fraction covered by, detn. of, in **computer**-assisted identification of **protein** with known three-dimensional **structure**)
- IT Escherichia coli  
(**ribose-binding** **protein** of, three-dimensional **structure** profile for, in compatible sequence detection)
- IT **Amino acids**, properties  
RL: PRP (Properties)  
(**structural** properties of, in **computer**-assisted identification of **protein** with three-dimensional **structure**)
- IT Actins  
Myoglobins  
RL: ANST (Analytical study)  
(three-dimensional **structure** profile for, in compatible sequence detection)
- IT Receptors  
RL: ANST (Analytical study)  
(cAMP, three-dimensional **structure** profile for, in compatible sequence detection)
- IT Mathematics  
(equations, in **computer**-assisted identification of **protein** with known three-dimensional **structure**)
- IT **Proteins**, specific or class  
RL: ANST (Analytical study)  
(**ribose-binding**, three-dimensional **structure** profile for, of Escherichia coli, in compatible sequence detection)
- IT 50-69-1, Ribose  
RL: ANST (Analytical study)  
(**binding** **protein** for, three-dimensional **structure** profile for, of Escherichia coli, in compatible sequence detection)
- IT 60-92-4, Cyclic-AMP  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(receptor, three-dimensional **structure** profile for, in

compatible sequence detection)

L86 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1992:545595 HCAPLUS

DN 117:145595

TI Microscopic **modeling** of **ligand** diffusion through the  
**protein** leghemoglobin: **computer simulations**  
and experiments

AU Verkhivker, Gennady; Elber, Ron; Gibson, Quentin H.

CS Dep. Chem., Univ. Illinois, Chicago, IL, 60680, USA

SO Journal of the American Chemical Society (1992), 114(20),  
7866-78

CODEN: JACSAT; ISSN: 0002-7863

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB The diffusion of carbon monoxide through lupine legHb was investigated. The potential of mean force, the transition-state theory rate const., the friction kernel, the transmission coeff., and the diffusion const. were calcd. The **computations** are based on previous exploration of the diffusion dynamics using the mean field method (LES) and on calcns. of the reaction **coordinate**. The back of the heme pocket (close to phenylalanine 44 and phenylalanine 29) is a shallow free energy min. for the dissoed. **ligand**. The min. is directly accessible (without a barrier) from the **binding** site. The barrier for escaping from the free energy min. to the CE loop is low (approx. 3 kcal/mol). Once the **ligand** leaves the pocket, the diffusion is barrierless. The **ligand** escapes in two steps. In the first (activated) step the **ligand** is hopping from the heme pocket to the **protein** interior, and in the **second** step it diffuses through the **protein** matrix to the **surface** of the macromol. The transition-state theory (which is appropriate for activated processes) is used for the first part of the process. For the **second** part a diffusion **model** is constructed. The calcd. friction kernel and its power spectrum strongly depend on the reaction **coordinate**. The power spectrum is consistent with previous interpretations of the diffusion dynamics. In the first step of the process the barrier is local and the power spectrum shows only high-frequency modes. In the **second** step significant coupling to low-frequency (extended) modes is obsd., and the diffusion **coordinate** is dominated by motions of the C and the G helices of the **protein**. Exptl. results for **ligand** rebinding kinetics in lupine legHb are reported. It is shown that different diat. **ligands** have an unusually fast diffusion rate in accord with theory.

ST **ligand** diffusion legHb; **simulation ligand**  
diffusion legHb

IT **Ligands**

RL: PEP (Physical, engineering or chemical process); PROC (Process)  
(diffusion of, in legHb interior, empirical and **mol.**  
**modeling** of)

IT Legoglobins

RL: BIOL (Biological study)  
(**ligand** diffusion through, empirical and **mol.**  
**modeling** of)

IT Free energy

(of diffusion, of **ligand** in legHb, empirical and theor.  
studies of)

IT Potential energy and function

(of **ligand** diffusion in leg Hb interior, empirical and  
**mol. modeling** of)

IT **Molecular modeling**

(of **ligand** diffusion in legHb interior)

IT Kinetics of recombination  
 (geminate, of **ligand binding** to legHb, **mol**  
 . **modeling** of diffusion in relation to)

IT **Conformation and Conformers**  
 (**helical**, of legHb, motions of, **ligand** diffusion  
 response to)

IT 630-08-0, Carbon monoxide, biological studies  
 RL: PEP (Physical, engineering or chemical process); PROC (Process)  
 (diffusion of, in legHb interior, theor. and empirical studies of)

IT 7782-44-7, Oxygen, reactions 10102-43-9, Nitric oxide, reactions  
 RL: PRP (Properties)  
 (geminate recombination kinetics of, with legHb of lupine, **mol**  
 . **modeling** of diffusion in relation to)

IT 14875-96-8, Heme  
 RL: BIOL (Biological study)  
 (**ligand** diffusion from, in legHb, empirical and **mol**  
 . **modeling** of)

L86 ANSWER 23 OF 26 HCAPLUS COPYRIGHT 2003 ACS

AN 1992:58326 HCAPLUS

DN 116:58326

TI System and method for determining three-dimensional **structures**  
 of **proteins**

IN Skolnick, Jeffrey

PA Scripps Clinic and Research Foundation, USA

SO PCT Int. Appl., 136 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM G06F015-46

CC 20-5 (History, Education, and Documentation)

Section cross-reference(s): 6, 9

FAN.CNT 1

|      | PATENT NO.   | KIND | DATE         | APPLICATION NO. | DATE         |
|------|--|------|--------------|-----------------|--------------|
| PI   | WO 9116683   | A1   | 19911031     | WO 1991-US2786  | 19910423 <-- |
|      | W: AU, CA, FI, JP, NO                                  |      |              |                 |              |
|      | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE |      |              |                 |              |
|      | AU 9178837   | A1   | 19911111     | AU 1991-78837   | 19910423 <-- |
|      | JP 05501324  | T2   | 19930311     | JP 1991-509821  | 19910423 <-- |
| PRAI | US 1990-513918   |      | 19900424 <-- |                 |              |
|      | WO 1991-US2786   |      | 19910423 <-- |                 |              |

AB The system comprises an input means such as a keyboard for specifying  
 (entering) selected **amino acid** sequences and other  
 data such as temp. and **fold** preferences, a RAM (random access  
 memory) for storing such data, a ROM (read-only memory) with a stored  
 program, a CRT (cathode ray tube) display unit and/or printer, an optional  
 auxiliary disk storage device for storage of relevant data bases, and a  
 microprocessor for processing the entered data, for **simulating**,  
 under control of the stored program, the **folding** of the  
**protein** from its unfolded state to its **folded** (tertiary)  
 state, and for displaying via the display unit (or printer) tertiary  
**conformations** of the **protein** in 3 dimensions. A block  
 diagram of the system, flow charts showing its method of operation, and  
**computer** code are included, as are graphical illustrations of a  
**folding** pathway defined by a sequence as it **folds** into  
 its native state.

ST **protein conformation computer**  
**modeling; folding protein computer**  
**modeling**

IT **Algorithm**

**Computer** program

(for **protein** three-dimensional **conformation** detn.)



- IT **Computer application**  
(in **protein** three-dimensional **conformation** detn.)
- IT **Molecular modeling**  
(of **protein** three-dimensional **conformation**,  
**computer** system for)
- IT **Conformation and Conformers**  
(**protein**, three-dimensional, detn. of, **computer**  
system for)
- IT **Proteins, biological studies**  
RL: PRP (Properties)  
(three-dimensional **conformation** of, detn. of,  
**computer** system for)
- IT **Simulation and Modeling, biological**  
(Monte Carlo, in **protein** three-dimensional  
**conformation** detn. with **computer** system)
- IT **Proteins, specific or class**  
RL: PRP (Properties)  
(globular, three-dimensional **conformation** of, detn. of,  
**computer** system for)
- L86 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2003 ACS
- AN 1989:402931 HCAPLUS
- DN 111:2931
- TI A multiple sequence alignment **algorithm** for homologous  
**proteins** using **secondary structure** information  
and optionally keying alignments to functionally important sites
- AU Henneke, Christina M.
- CS Sch. Chem., Univ. Bath, Bath, BA2 7AY, UK
- SO CABIOS, Computer Applications in the Biosciences (1989), 5(2),  
141-50  
CODEN: COABER; ISSN: 0266-7061
- DT Journal
- LA English
- CC 6-3 (General Biochemistry)  
Section cross-reference(s): 9
- AB The programs described herein function as part of a suite of programs  
**designed** for pairwise alignment, multiple alignment, generation of  
randomized sequences, prodn. of alignment scores, and a sorting routine  
for anal. of the alignments produced. The sequence alignment programs  
penalize gaps (absences of residues) within regions of **protein**  
**secondary structure** and have the added option of  
fingerprinting **structurally** or functionally important  
**protein** residues. The multiple alignment program is based upon  
the sequence alignment method of Needleman and Wunsch and the multiple  
alignment extension of Barton and Sternberg. Application includes the  
feature of optionally weighting active site, monomer-monomer,  
**ligand** contact, or other important template residues to bias the  
alignment toward matching these residues. A sum-score for the alignments  
is introduced, which is independent of gap penalties. This score more  
adequately reflects the character of the alignments for a given scoring  
matrix than the gap-penalty-dependent total score described previously in  
the literature. In addn., individual **amino acid**  
similarity scores at each residue position in the alignments are printed  
with the alignment output to enable immediate quant. assessment of homol.  
at key sections of the aligned chains.
- ST **protein** sequence alignment **conformation**  
**computer algorithm**
- IT **Protein sequences**  
(alignment of, of homologous **proteins**, **algorithm**  
using **secondary conformation** and functional sites  
for)
- IT **Algorithm**  
(for **protein** sequence alignment, using **secondary**

- conformation and functional sites)  
IT **Conformation and Conformers**  
(secondary, of proteins, in amino  
acid sequence alignment algorithm)
- L86 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2003 ACS  
AN 1986:144994 HCAPLUS  
DN 104:144994  
TI Comparative evaluation of the effectiveness of predicting the  
secondary structure of simple and ligand  
-containing proteins  
AU Barkovskii, E. V.  
CS Inst. Zool., Minsk, USSR  
SO Vestsi Akademii Navuk BSSR, Seryya Biyalagichnykh Navuk (1985),  
(5), 109-10  
CODEN: VABBA3; ISSN: 0002-3558  
DT Journal  
LA Russian  
CC 9-10 (Biochemical Methods)  
Section cross-reference(s): 6, 7  
AB The effectiveness of 3 previously published algorithms for  
predicting the conformation of 3 classes of proteins  
was investigated. The protein classes studied were (1)  
nucleotide-binding proteins (lactate dehydrogenase,  
alc. dehydrogenase, etc.), (2) metalloproteins (Hb, cytochromes,  
etc.), and (3) simple proteins (lysozyme, RNase, etc.). The  
accuracy of prediction depended on the algorithm used and the  
class of proteins. In general, the prediction was more accurate  
for simple proteins than for the other 2 classes.  
ST conformation prediction protein ligand  
algorithm; nucleotide binding protein  
conformation prediction; metalloprotein  
conformation prediction; enzyme conformation  
prediction algorithm  
IT **Enzymes**  
**Proteins**  
RL: PRP (Properties)  
(conformation of, prediction of)  
IT **Algorithm**  
(for conformational prediction of proteins,  
accuracy of)  
IT **Conformation and Conformers**  
(of proteins, prediction of, protein classes in  
relation to)  
IT **Enzymes**  
**Proteins**  
RL: PRP (Properties)  
(metallo-, conformation of, prediction of)  
IT **Enzymes**  
**Proteins**  
RL: PRP (Properties)  
(nucleotide-binding, conformation of, prediction  
of)
- L86 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2003 ACS  
AN 1986:105613 HCAPLUS  
DN 104:105613  
TI **Molecular speleology: the exploration of crevices in**  
**proteins for prediction of binding sites, design**  
**of drugs and analysis of surface recognition**  
AU Lesk, Arthur M.  
CS Lab. Mol. Biol., MRC, Cambridge, CB2 2QH, UK  
SO Acta Crystallographica, Section A: Foundations of Crystallography (

1986), A42(2), 83-5  
CODEN: ACACEQ; ISSN: 0108-7673

DT Journal  
LA English  
CC 9-10 (Biochemical Methods)  
Section cross-reference(s): 1

AB A method is described for analyzing **mol. surface** complementarity, including the **binding** of **ligands** to **proteins** or the interaction of elements of **secondary structure** in **protein** interiors. A **computer** program can identify and **model mols.** that satisfy general criteria for good **binding** affinity. **Computational** tests are presented. This approach is likely to have useful application in the anal. of **surface recognition** in **proteins**, including the identification of **binding** sites, and in the **design** of drugs for specific targets, by (i) suggesting potential pharmacophores to the medicinal chemist for further **computational** anal. or lab. testing, (ii) suggestion of derivs. of a known **ligand** to enhance its affinity, or (iii) searching a data base of known drugs for a match to the predicted **ligand**.

ST **protein surface** complementarity analysis;  
**ligand binding protein** prediction; drug  
**design protein surface; computer**  
program **protein surface** complementarity

IT **Ligands**  
RL: ANST (Analytical study)  
(**binding** of, to **proteins**, method for  
**surface** complementarity anal. in study of)

IT Pharmaceuticals  
(**design** of, method for **protein surface**  
complementarity anal. for)

IT **Computer** program  
(for **protein surface** complementarity anal.)

IT **Surface structure**  
(of **proteins**, complementarity of, method for study of)

IT **Proteins**  
RL: ANST (Analytical study)  
(**surface** complementarity of, method for study of)

IT **Computer application**  
(to **protein surface** complementarity anal.)

=> fil medline

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=> d all tot

L125 ANSWER 1 OF 19 MEDLINE

AN 2002116670 MEDLINE

DN 21825961 PubMed ID: 11836225

TI Prediction of 3D neighbours of molecular surface patches in proteins by

artificial neural networks.

AU Dietmann S; **Frommel C**  
 CS Medical Faculty of the Humboldt University, (Charite) Institute of Biochemistry, Monbijoustr. 2A, Berlin D-10117, Germany..  
 dietmann@ebi.ac.uk  
 SO BIOINFORMATICS, (2002 Jan) 18 (1) 167-74.  
 Journal code: 9808944. ISSN: 1367-4803.  
 CY England: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200206  
 ED Entered STN: 20020220  
 Last Updated on STN: 20020611  
 Entered Medline: 20020610

AB MOTIVATION: Molecular Surface Patches (MSPs) of proteins are responsible for selective interactions between internal parts of one protein molecule or between protein and other molecules. The prediction of the neighbours of a distinct Secondary Structural Element (SSE) would be an important step for protein structure prediction. RESULTS: Based on a computational analysis of complementary molecular patches of SSEs, feed-forward Neural Networks (NNs) are trained on a large set of helices for predicting the neighbours of given MSPs. Accuracy of prediction is 96% if only two types of neighbours: solvent or protein are considered, yet drops to 81% for three types of neighbours: (1) solvent, (2) helix/strand or (3) coil. Implications of the method for the prediction of protein structure and subunit interaction are discussed. As a special test case, the structurally equivalent helices of monomeric myoglobin and the homologous subunits of tetrameric haemoglobin are compared.

CT Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't  
 Computational Biology  
 Hemoglobins: CH, chemistry  
 Models, Molecular  
 Myoglobin: CH, chemistry  
 \*Neural Networks (Computer)  
 Protein Conformation  
**Protein Structure, Secondary**  
 Protein Subunits  
 \*Proteins: CH, chemistry  
 Surface Properties

CN 0 (Hemoglobins); 0 (Myoglobin); 0 (Protein Subunits); 0 (Proteins)

L125 ANSWER 2 OF 19 MEDLINE  
 AN **2002048829** MEDLINE  
 DN **21632016** PubMed ID: **11776292**  
 TI Matching organic libraries with protein-substructures.  
 AU **Preissner R; Goede A; Rother K; Osterkamp F; Koert U; Froemmel C**  
 CS Institute of Biochemistry, Charite, Medical Faculty of the Humboldt-University, Berlin, Germany..  
 SO JOURNAL OF COMPUTER-AIDED MOLECULAR DESIGN, (2001 Sep) 15 (9) 811-7.  
 Journal code: 8710425. ISSN: 0920-654X.  
 CY Netherlands  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200206  
 ED Entered STN: 20020125  
 Last Updated on STN: 20020611  
 Entered Medline: 20020610

AB We present a general approach which allows automatic identification of sub-structures in proteins that resemble given three-dimensional templates. This paper documents its success with non-peptide templates

such as beta-turn mimetics. We considered well-tested turn-mimetics such as the bicyclic turned dipeptide (BTD), spiro lactam (Spiro) and the 2,5-disubstituted tetrahydrofuran (THF), a new furan-derivative which was recently developed and characterized. The detected geometric similarity between the templates and the protein patches corresponds to r.m.s.-values of 0.3 Å for more than 80% of the constituting atoms, which is typical for active site comparisons of homologous proteins. This fast automatic procedure might be of biomedical value for finding special mimicking leads for particular protein sub-structures as well as for template-assembled synthetic protein (TASP) design.

CT Computer Simulation

Databases, Protein

\*Drug Design

Models, Molecular

\*Molecular Mimicry

Molecular Structure

Peptide Library

**Protein Binding**

\*Proteins: CH, chemistry

CN 0 (Peptide Library); 0 (Proteins)

L125 ANSWER 3 OF 19 MEDLINE

AN 2000304908 MEDLINE

DN 20304908 PubMed ID: 10843865

TI Conservation of substructures in proteins: interfaces of secondary structural elements in proteasomal subunits.

AU Gille C; Goede A; Preissner R; Rother K; Frommel

C

CS Institute of Biochemistry Charite, Medical Faculty of the Humboldt University, Monbijoustrasse 2a, Berlin, 10117, Germany.. christoph.gille@charite.de

SO JOURNAL OF MOLECULAR BIOLOGY, (2000 Jun 16) 299 (4) 1147-54.

Journal code: 2985088R. ISSN: 0022-2836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Space Life Sciences

EM 200007

ED Entered STN: 20000720

Last Updated on STN: 20000720

Entered Medline: 20000712

AB It is observed that during divergent evolution of two proteins with a common phylogenetic origin, the structural similarity of their backbones is often preserved even when the sequence similarity between them decreases to a virtually undetectable level. Here we analyzed, whether the conservation of structure along evolution involves also the local atomic structures in the interfaces between secondary structural elements. We have used as study case one protein family, the proteasomal subunits, for which 17 crystal structures are known. These include 14 different subunits of *Saccharomyces cerevisiae*, 2 subunits of *Thermoplasma acidophilum* and one subunit of *Escherichia coli*. The structural core of the 17 proteasomal subunits has 23 secondary structural elements. Any two adjacent secondary structural elements form a molecular interface consisting of two molecular patches. We found 61 interfaces that occurred in all 17 subunits. The 3D shape of equivalent molecular patches from different proteasomal subunits were compared by superposition. Our results demonstrate that pairs of equivalent molecular patches show an RMSD which is lower than that of randomly chosen patches from unrelated proteins. This is true even when patch comparisons with identical residues were excluded from the analysis. Furthermore it is known that the sequential dissimilarity is correlated to the RMSD between the backbones of the members of protein families. The question arises whether this is also true for local atomic structures. The results show that the

correlation of individual patch RMSD values and local sequence dissimilarities is low and has a wide range from 0 to 0.41, however, it is surprising that there is a good correlation between the average RMSD of all corresponding patches and the global sequence dissimilarity. This average patch RMSD correlates slightly stronger than the C(alpha)-trace RMSD to the global sequence dissimilarity.

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CT Algorithms

Amino Acid Sequence

**Binding Sites**

\*Conserved Sequence

\*Cysteine Endopeptidases: CH, chemistry

\*Cysteine Endopeptidases: ME, metabolism

**Databases, Factual**

Escherichia coli: EN, enzymology

Evolution, Molecular

Models, Molecular

\*Multienzyme Complexes: CH, chemistry

\*Multienzyme Complexes: ME, metabolism

Protein Structure, Quaternary

**Protein Structure, Secondary**

Saccharomyces cerevisiae: EN, enzymology

Sequence Alignment

Software

Thermoplasma: EN, enzymology

CN 0 (Multienzyme Complexes); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.99.46 (multicatalytic endopeptidase complex)

L125 ANSWER 4 OF 19 MEDLINE

AN 2000169613 MEDLINE

DN 20169613 PubMed ID: 10705435

TI Homonyms and synonyms in the Dictionary of Interfaces in Proteins (DIP).

AU Preissner R; Goede A; Frommel C

CS Medical Faculty, Humboldt University, Charite, Institute of Biochemistry, Berlin, Germany.. preissner@rz.hu-berlin.de

SO BIOINFORMATICS, (1999 Oct) 15 (10) 832-6.

Journal code: 9808944. ISSN: 1367-4803.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200004

ED Entered STN: 20000421

Last Updated on STN: 20000421

Entered Medline: 20000411

AB MOTIVATION: Should reports on molecular mimicry in particular cases, e.g. responsible for cross-reactivity, be considered as accidental or as a general principle in protein evolution? To answer this question, two types of similarity have to be considered: those in homologues (synonyms) and resemblance between patches from unrelated proteins (homonyms). RESULTS: All interfaces from known protein structures were collected in a comprehensive data bank [Dictionary of Interfaces in Proteins (DIP)]. A fast, sequence-independent, three-dimensional superposition procedure was developed to search automatically for geometrically similar surface areas. Surprisingly, we found a large number of structurally similar interfaces on the surface of unrelated proteins. Even patches from different types of secondary structure were found resembling each other. The putative functional meaning of homonyms is demonstrated with striking examples.

CT Check Tags: Comparative Study

Algorithms

Amino Acid Sequence

Computational Biology

\*Databases, Factual

\*Dictionaries, Chemical  
Models, Molecular  
Molecular Mimicry  
Molecular Sequence Data  
Protein Conformation  
\*Proteins: CH, chemistry  
\*Proteins: GE, genetics

CN 0 (Proteins)

L125 ANSWER 5 OF 19 MEDLINE

AN 2000027473 MEDLINE

DN 20027473 PubMed ID: 10556242

TI Spare parts for helix-helix interaction.

AU Preissner R; Goede A; Frommel C

CS Institute of Biochemistry, Charite, Medical Faculty of the Humboldt  
University, Monbijoustr 2, 10117 Berlin, Germany.

SO PROTEIN ENGINEERING, (1999 Oct) 12 (10) 825-32.

Journal code: 8801484. ISSN: 0269-2139.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200001

ED Entered STN: 20000124

Last Updated on STN: 20000124

Entered Medline: 20000112

AB About 6000 contact regions (patches) of helix-to-helix packing from 300  
well-resolved non-homologous protein structures were considered. The  
patches were defined by the spatial helical neighbors and were estimated  
in atomic detail using a variable distance criterion. The following  
questions are addressed. (1) Are the amino acid preferences and atomic  
composition of distinct types of helical patches indicative for the type  
of their neighbor? Distributions of size, atomic composition and packing  
density are compared for different types of helical interfaces. Thereby  
contact preferences are derived for parts of secondary structures  
adjoining each other or pointing towards the solvent. (2) Is it possible  
to cluster helical patches according to their structural similarity? For  
these purposes the patches were classified with an automatic  
sequence-independent superposition procedure which yields a distinctively  
reduced set of representative interfaces. On this basis, the methodology  
for finding exchangeable patches in different proteins is demonstrated.

CT Databases, Factual

Models, Molecular

Protein Folding

\*Protein Structure, Secondary

\*Proteins: CH, chemistry

\*Proteins: ME, metabolism

CN 0 (Proteins)

L125 ANSWER 6 OF 19 MEDLINE

AN 1999342043 MEDLINE

DN 99342043 PubMed ID: 10411900

TI A systematic study of low-resolution recognition in protein--protein  
complexes.

AU Vakser I A; Matar O G; Lam C F

CS Department of Cell and Molecular Pharmacology, Medical University of South  
Carolina, 171 Ashley Avenue, Charleston, SC 29425, USA.. vakseri@muscd.edu

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF  
AMERICA, (1999 Jul 20) 96 (15) 8477-82.

Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals  
 EM 199908  
 ED Entered STN: 19990910  
 Last Updated on STN: 19990910  
 Entered Medline: 19990823

AB A comprehensive nonredundant database of 475 cocrystallized protein-protein complexes was used to study low-resolution recognition, which was reported in earlier docking experiments with a small number of proteins. The docking program GRAMM was used to delete the atom-size structural details and systematically dock the resulting molecular images. The results reveal the existence of the low-resolution recognition in 52% of all complexes in the database and in 76% of the 113 complexes with an interface area >4,000 Å<sup>2</sup>. Limitations of the docking and analysis tools used in this study suggest that the actual number of complexes with the low-resolution recognition is higher. However, the results already prove the existence of the low-resolution recognition on a broad scale.

CT Check Tags: Support, U.S. Gov't, Non-P.H.S.

Algorithms  
 Binding Sites  
 Crystallization  
 Databases  
 Fourier Analysis  
 Ligands  
 Models, Molecular  
 Protein Binding  
 Protein Structure, Secondary  
 Protein Structure, Tertiary  
 \*Proteins: CH, chemistry  
 Receptors, Cell Surface: CH, chemistry

CN 0 (Ligands); 0 (Proteins); 0 (Receptors, Cell Surface)

L125 ANSWER 7 OF 19 MEDLINE

AN 1999180410 MEDLINE

DN 99180410 PubMed ID: 10082373

TI Enzyme-mononucleotide interactions: three different folds share common structural elements for ATP recognition.

AU Denessiouk K A; Lehtonen J V; Johnson M S

CS Department of Biochemistry and Pharmacy, Abo Akademi University, Turku, Finland.

SO PROTEIN SCIENCE, (1998 Aug) 7 (8) 1768-71.  
 Journal code: 9211750. ISSN: 0961-8368.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199905

ED Entered STN: 19990601  
 Last Updated on STN: 19990601  
 Entered Medline: 19990519

AB Three ATP-dependent enzymes with different folds, cAMP-dependent protein kinase, D-Ala:D-Ala ligase and the alpha-subunit of the alpha2beta2 ribonucleotide reductase, have a similar organization of their ATP-binding sites. The most meaningful similarity was found over 23 structurally equivalent residues in each protein and includes three strands each from their beta-sheets, in addition to a connecting loop. The equivalent secondary structure elements in each of these enzymes donate four amino acids forming key hydrogen bonds responsible for the common orientation of the "AMP" moieties of their ATP-ligands. One lysine residue conserved throughout the three families binds the alpha-phosphate in each protein. The common fragments of structure also position some, but not all, of the equivalent residues involved in hydrophobic contacts with the adenine ring. These examples of convergent evolution reinforce the view that different proteins can fold in different ways to produce similar



structures locally, and nature can take advantage of these features when structure and function demand it, as shown here for the common mode of ATP-binding by three unrelated proteins.

CT Check Tags: Support, Non-U.S. Gov't

Adenine: CH, chemistry

\*Adenosine Triphosphate: CH, chemistry

Allosteric Site

Computer Simulation

Cyclic AMP-Dependent Protein Kinases: CH, chemistry

Databases, Factual

\*Enzymes: CH, chemistry

Models, Molecular

\*Nucleotides: CH, chemistry

Peptide Synthases: CH, chemistry

Phosphates: CH, chemistry

Protein Binding

Protein Structure, Secondary

Ribonucleotide Reductases: CH, chemistry

Ribose: CH, chemistry

RN 50-69-1 (Ribose); 56-65-5 (Adenosine Triphosphate); 73-24-5 (Adenine)

CN 0 (Enzymes); 0 (Nucleotides); 0 (Phosphates); EC 1.17.4 (Ribonucleotide Reductases); EC 2.7.1.37 (Cyclic AMP-Dependent Protein Kinases); EC 6.3.2. (Peptide Synthases); EC 6.3.2.4 (D-alanylalanine synthetase)

L125 ANSWER 8 OF 19 MEDLINE

AN 1999077019 MEDLINE

DN 99077019 PubMed ID: 9862203

TI Sequences annotated by structure: a tool to facilitate the use of structural information in sequence analysis.

AU Milburn D; Laskowski R A; Thornton J M

CS Department of Biochemistry and Molecular Biology, University College, London, UK.

SO PROTEIN ENGINEERING, (1998 Oct) 11 (10) 855-9.

Journal code: 8801484. ISSN: 0269-2139.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199903

ED Entered STN: 19990316

Last Updated on STN: 20000303

Entered Medline: 19990303

AB With the aim of bridging the gap between protein sequence and structural analyses, we have developed a tool to aid the identification of new protein sequences by recognizing distant homologues using structural information. The tool generates sequence annotated by structure (SAS) files, applying structural information derived from structural analyses to a given protein sequence. A World Wide Web interface allows a given sequence to be submitted either for structural annotation or, where its structure is unknown, for search and alignment against sequences of known structure. In both cases, SAS will colour residues in the sequence of known structure according to a selection of properties, including secondary structure, interatomic contacts and active site information. SAS can also be used to inspect properties of a single structure.

CT Check Tags: Support, Non-U.S. Gov't

Amino Acid Sequence

Binding Sites

DNA-Binding Proteins: CH, chemistry

Databases, Factual

Hydrogen Bonding

\*Internet

Lactalbumin: CH, chemistry

Lactalbumin: ME, metabolism

**Ligands**

Metals: ME, metabolism

**Molecular Sequence Data**

Muramidase: CH, chemistry

Muramidase: ME, metabolism

**\*Protein Conformation**

Protein Folding

**Protein Structure, Secondary****\*Proteins: CH, chemistry**

Sequence Alignment

**\*Sequence Analysis**

Sequence Homology, Amino Acid

**Software**

Structure-Activity Relationship

RN 9013-90-5 (Lactalbumin)

CN 0 (DNA-Binding Proteins); 0 (**Ligands**); 0 (Metals); 0 (Proteins);

EC 3.2.1.17 (Muramidase)

L125 ANSWER 9 OF 19 MEDLINE

AN 1999000702 MEDLINE

DN 99000702 PubMed ID: 9784114

TI CoMFA-based prediction of agonist affinities at recombinant D1 vs D2 dopamine receptors.

AU Wilcox R E; Tseng T; Brusniak M Y; Ginsburg B; Pearlman R S; Teeter M; DuRand C; Starr S; Neve K A

CS Molecular Pharmacology Laboratory, College of Pharmacy, University of Texas at Austin, Austin, Texas 78712-1074, USA..

wilcoxrich@mail.utexas.edu

NC RR08579A (NCRR)

SO JOURNAL OF MEDICINAL CHEMISTRY, (1998 Oct 22) 41 (22) 4385-99.

Journal code: 9716531. ISSN: 0022-2623.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199811

ED Entered STN: 19990106

Last Updated on STN: 19990106

Entered Medline: 19981123

AB We have previously shown that using agonist affinity at recombinant receptors selectively expressed in clonal cells as the dependent variable in three-dimensional quantitative structure-activity relationship studies (3D-QSAR) presents a unique opportunity for accuracy and precision in measurement. Thus, a comparison of affinity's structural determinants for a set of compounds at two different recombinant dopamine receptors represents an attainable goal for 3D-QSAR. A molecular database of bound conformations of 16 structurally diverse agonists was established by alignment with a high-affinity template compound for the D1 receptor, 3-allyl-6-bromo-7,8-dihydroxy-1-phenyl-2,3,4, 5-tetrahydro-1H-benzazepin. A second molecular database of the bound conformations of the same compounds was established against a second template for the D2 receptor, bromocriptine. These aligned structures suggested three-point pharmacophore maps (one cationic nitrogen and two electronegative centers) for the two dopamine receptors, which differed primarily in the height of the nitrogen above the plane of the catechol ring and in the nature of the hydrogen-bonding region. The  $\ln(1/KL)$  values for the low-affinity agonist binding conformation at recombinant D1 and D2 dopamine receptors stably expressed in C6 glioma cells were used as the target property for the CoMFA (comparative molecular field analysis) of the 16 aligned structures. The resulting CoMFA models yielded cross-validated  $R^2$  ( $q^2$ ) values (standard error of prediction) of 0.879 (1.471, with five principal components) and 0.834 (1.652, with five principal components) for D1 and D2 affinity, respectively. The simple  $R^2$  values (standard error of the

estimate) were 0.994 (0.323) and 0.999 (0.116), respectively, for D1 and D2 receptor. F values were 341 and 2465 for D1 and D2 models, respectively, with 5 and 10 df. The predictive utility of the CoMFA model was evaluated at both receptors using the dopamine agonists, apomorphine and 7-OH-DPAT. Predictions of KL were accurate at both receptors. Flexible 3D searches of several chemical databases (NCI, MDDR, CMC, ACD, and Maybridge) were done using basic pharmacophore models at each receptor to determine the similarity of hit lists between the two models. The D1 and D2 models yielded different lists of lead compounds. Several of the lead compounds closely resembled high-affinity training set compounds. Finally, homology modeling of agonist binding to the D2 receptor revealed some consistencies and inconsistencies with the CoMFA-derived D2 model and provided a possible rationale for features of the D2 CoMFA contour map. Together these results suggest that CoMFA-homology based models may provide useful insights concerning differential agonist-receptor interactions at related receptors. The results also suggest that comparisons of CoMFA models for two structurally related receptors may be a fruitful approach for differential QSAR.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

#### Binding Sites

##### Databases, Factual

\*Dopamine Agonists: CH, chemistry  
Dopamine Agonists: ME, metabolism  
Dopamine Agonists: PD, pharmacology

##### Ligands

Macaca mulatta

##### \*Models, Molecular

##### Molecular Conformation

##### Protein Structure, Secondary

Rats

\*Receptors, Dopamine D1: AG, agonists  
Receptors, Dopamine D1: BI, biosynthesis  
Receptors, Dopamine D1: CH, chemistry  
Receptors, Dopamine D1: ME, metabolism  
\*Receptors, Dopamine D2: AG, agonists  
Receptors, Dopamine D2: BI, biosynthesis  
Receptors, Dopamine D2: CH, chemistry  
Receptors, Dopamine D2: ME, metabolism  
Recombinant Proteins: AG, agonists  
Recombinant Proteins: CH, chemistry  
Recombinant Proteins: ME, metabolism

Structure-Activity Relationship

Tumor Cells, Cultured

CN 0 (Dopamine Agonists); 0 (Ligands); 0 (Receptors, Dopamine D1);  
0 (Receptors, Dopamine D2); 0 (Recombinant Proteins)

L125 ANSWER 10 OF 19 MEDLINE

AN 1998417653 MEDLINE

DN 98417653 PubMed ID: 9743635

TI Supersites within superfolds. Binding site similarity in the absence of homology.

AU Russell R B; Sasieni P D; Sternberg M J

CS Biomolecular Modelling Laboratory, Lincoln's Inn Fields, PO Box 123, London WC2A 3PX, UK.

SO JOURNAL OF MOLECULAR BIOLOGY, (1998 Oct 2) 282 (4) 903-18.

Journal code: 2985088R. ISSN: 0022-2836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Space Life Sciences

EM 199907

ED Entered STN: 19990727

Last Updated on STN: 19990727

Entered Medline: 19990712

AB A method is presented to assess the significance of binding site similarities within superimposed protein three-dimensional (3D) structures and applied to all similar structures in the Protein Data Bank. For similarities between 3D structures lacking significant sequence similarity, the important distinction was made between remote homology (an ancient common ancestor) and analogy (likely convergence to a folding motif) according to the structural classification of proteins (SCOP) database. Supersites were defined as structural locations on groups of analogous proteins (i.e. superfolds) showing a statistically significant tendency to bind substrates despite little evidence of a common ancestor for the proteins considered. We identify three potentially new superfolds containing supersites: ferredoxin-like folds, four-helical bundles and double-stranded beta helices. In addition, the method quantifies binding site similarities within homologous proteins and previously identified supersites such as that found in the beta/alpha (TIM) barrels. For the nine superfolds, the accuracy of predictions of binding site locations is assessed. Implications for protein evolution, and the prediction of protein function either through fold recognition or tertiary structure comparison, are discussed.

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CT Check Tags: Animal; Human; Support, Non-U.S. Gov't

\*Binding Sites

\*Databases, Factual

Evolution, Molecular

Ferredoxins: ME, metabolism

Ligands

Models, Molecular

Protein Conformation

\*Protein Folding

Protein Structure, Secondary

\*Proteins: CH, chemistry

Proteins: ME, metabolism

Sequence Alignment

Sequence Homology, Amino Acid

Statistical Distributions

Structure-Activity Relationship

CN 0 (Ferredoxins); 0 (Ligands); 0 (Proteins)

L125 ANSWER 11 OF 19 MEDLINE

AN 1998332753 MEDLINE

DN 98332753 PubMed ID: 9665855

TI Dictionary of interfaces in proteins (DIP). Data bank of complementary molecular surface patches.

AU Preissner R; Goede A; Frommel C

CS Institute of Biochemistry, Medical Faculty of the Humboldt University (Charite), Monbijoustr. 2A, Berlin, D-10117, Germany.

SO JOURNAL OF MOLECULAR BIOLOGY, (1998 Jul 17) 280 (3) 535-50.

Journal code: 2985088R. ISSN: 0022-2836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199808

ED Entered STN: 19980820

Last Updated on STN: 19980820

Entered Medline: 19980807

AB Molecular surface areas of proteins are responsible for selective binding of **ligands** and protein-protein recognition, and are considered the basis for specific interactions between different parts of a protein. This basic principle leads us to study the interfaces within proteins as a

learning set for intermolecular recognition processes of **ligands** like substrates, coenzymes, etc., and for prediction of contacts occurring during protein folding and association. For this purpose, we defined interfaces as pairs of matching molecular surface patches between neighboring secondary structural elements. All such interfaces from known protein structures were collected in a comprehensive data bank of interfaces in proteins (DIP). The up-to-date DIP contains interface files for 351 selected Brookhaven Protein Data Bank entries with a total of about 160,000 surface elements formed by 12,475 secondary structures. For special purposes, the inclusion of additional structures or selection of subgroups of proteins can be performed in an easy and straightforward manner. Atomic coordinates of the constituents of molecular surface patches are directly accessible as well as the corresponding contact distances from given atoms to their neighboring secondary structural elements. As a rule, independent of the type of secondary structure, the molecular surface patches of the secondary structural elements can be described as quite flat bodies with a length to width to depth ratio of about 3:2:1 for patches consisting of more than ten atoms. The relative orientation between two docking patches is strongly restricted, due to the narrow distribution of the distances between their centers of mass and of the angles between their normal lines, respectively. The existing retrieval system for the DIP allows selection (out of the set of molecular patches) according to different criteria, such as geometric features, atomic composition, type of secondary structure, contacts, etc. A fast, sequence-independent 3-D superposition procedure was developed for automatic searches for geometrically similar surface areas. Using this procedure, we found a large number of structurally similar interfaces of up to 30 atoms in completely unrelated protein structures.

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CT **\*Databases, Factual**  
 Forecasting  
**Models, Molecular**  
 Protein Folding  
**Protein Structure, Secondary**  
**\*Proteins: CH, chemistry**  
 Solvents: CH, chemistry  
 Surface Properties  
 CN 0 (Proteins); 0 (Solvents)

L125 ANSWER 12 OF 19 MEDLINE

AN 1998075920 MEDLINE

DN 98075920 PubMed ID: 9415438

TI Applying experimental data to protein fold prediction with the genetic algorithm.

AU Dandekar T; Argos P

CS European Molecular Biology Laboratory, Heidelberg, Germany.

SO PROTEIN ENGINEERING, (1997 Aug) 10 (8) 877-93.

Journal code: 8801484. ISSN: 0269-2139.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199802

ED Entered STN: 19980224

Last Updated on STN: 19980224

Entered Medline: 19980211

AB Specific residue interactions as revealed from a few and readily available experiments can be quite important in shaping a protein's tertiary topology by complementing basic and general folding principles. This experimental information is employed in structure prediction (mainchain topology) based on sequence knowledge and the genetic algorithm with its ability to optimize simultaneously many parameters. Examples investigated include the distribution of cysteinyl S-S bonds, protein side-chain

**ligands** to iron-sulfur cages, cofactor-**ligands**, crosslinks amongst side-chains, and conserved hydrophobic and catalytic residues. Such interactions yield an improvement in the predicted topology (0.4-6.6 Å root mean square deviation in the positions of the backbone C alpha-atoms relative to those observed) compared with those resulting from simulations relying only on basic protein folding principles. For several examples the resultant topology depended critically on knowledge of the few and specific interactions such that the relationship between predicted and observed C alpha-positions was near random without their use. The combined methodology (experimental data and the genetic algorithm) should prove helpful in settings where experiment and theory can cooperate in successive steps to elucidate an unknown structure.

CT **\*Algorithms**

**Computer Simulation**

**Databases, Factual**

Disulfides: CH, chemistry

Evolution, Molecular

**Models, Molecular**

\*Protein Folding

**Protein Structure, Secondary**

**Protein Structure, Tertiary**

\*Proteins: CH, chemistry

**Proteins: GE, genetics**

CN 0 (Disulfides); 0 (Proteins)

L125 ANSWER 13 OF 19 MEDLINE

AN **97459773** MEDLINE

DN **97459773** PubMed ID: **9315733**

TI Inverse sequence similarity in proteins and its relation to the three-dimensional fold.

AU **Preissner R; Goede A; Michalski E; Frommel C**

CS Institute of Biochemistry, Charite, Berlin, Germany.

SO FEBS LETTERS, (1997 Sep 8) 414 (2) 425-9.

Journal code: 0155157. ISSN: 0014-5793.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199710

ED Entered STN: 19971105

Last Updated on STN: 19971105

Entered Medline: 19971021

AB Nowadays the most successful strategy for the prediction of the tertiary structure of proteins is the homology-based modelling using known structures. A real chance to predict the general fold of a protein arises only in cases with a sufficient sequence homology (e.g. 27% over 100 residues). In this analysis we examine the phenomenon of inverse sequence similarity (ISS) in proteins and its structural meaning. In sequence data bases we found a lot of examples for ISS up to 34% identity over 204 residues and a surprisingly large number of self-inverse protein sequences. By inspection of inverse similar sequence pairs with known tertiary structures we observe that inverse sequence alignments above the threshold indicating structural similarity generally do not imply comparable folds for both. From our analysis we conclude that the straightforward employment of ISS for protein structure prediction fails even above the known threshold for 'safe similarity'.

CT **\*Amino Acid Sequence**

**\*Computer Simulation**

Enzymes: CH, chemistry

Information Systems

\*Models, Molecular

Molecular Sequence Data

\*Protein Folding  
\*Protein Structure, Tertiary  
\*Proteins: CH, chemistry  
Ribonucleases: CH, chemistry  
Sequence Alignment

CN 0 (Enzymes); 0 (Proteins); EC 3.1.- (Ribonucleases)

L125 ANSWER 14 OF 19 MEDLINE

AN 96407680 MEDLINE

DN 96407680 PubMed ID: 8811733

TI Prediction of secondary structural content of proteins from their amino acid composition alone. II. The paradox with secondary structural class.

AU Eisenhaber F; Frommel C; Argos P

CS Institut für Biochemie der Charité, Medizinische Fakultät, Humboldt-Universität zu Berlin, Berlin-Mitte, Germany.

SO PROTEINS, (1996 Jun) 25 (2) 169-79.

Journal code: 8700181. ISSN: 0887-3585.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199612

ED Entered STN: 19970128

Last Updated on STN: 19970128

Entered Medline: 19961205

AB The success rates reported for secondary structural class prediction with different methods are contradictory. On one side, the problem of recognizing the secondary structural class of a protein knowing only its amino acid composition appears completely solved by simply applying jury decision with an elliptically scaled distance function. Chou and coworkers repeatedly (see Crit. Rev. Biochem. Mol. Biol. 30:275-349, 1995) published prediction accuracies near 100%. On the other hand, traditional secondary structure prediction techniques achieve success rates of about 70% for the secondary structural state per residue and about 75% for structural class only with extensive input information (full sequence of the query protein, its amino acid composition and length, multiple alignments with homologous sequences). In this article, we resolve the paradox and consider (1) the question of the secondary structural class definition, (2) the role of the representativity of the test set of protein tertiary structure for the current state of the Protein Data Bank (PDB); and (3) we estimate the real impact of amino acid composition on secondary structural class. We formulate three objective criteria for a reasonable definition of secondary structural classes and show that only the criterion of Nakashima et al. (J. Biochem. 99:153-162, 1986) complies with all of them. Only this definition matches the distribution of secondary structural content in representative PDB subsets, whereas other criteria leave many proteins (up to 65% of all PDB entries) simply unassigned. We review critically specialized secondary-structural class prediction methods, especially those of Chou and coworkers, which claim almost 100% accuracy using only amino acid composition, and resolve the paradox that these prediction accuracies are better than those from secondary structure predictions from multiple alignments. We show (i) that these techniques rely on a preselection of test sets which removes irregular proteins and other proteins without any class assignment (about 35% of all PDB entries); and (ii) that even for preselected representative test sets, the success rate drops to 60% and lower for a 4-type classification (alpha, beta, alpha + beta, alpha/beta). The prediction accuracies fall to about 50% if the secondary structural class definition of Nakashima et al. is applied and only few irregular proteins are preselected and removed from automatically generated, representative subsets of the PDB. We have applied two new vector decomposition methods for secondary structural content prediction from amino acid composition alone, with and without consideration of amino acid

compositional coupling in the learning set of tertiary structures respectively, to the problem of class prediction and achieve about 60% correct assignment among four classes (alpha, beta, mixed, irregular) as well as single sequence-based secondary structure prediction methods like GORIII and COMBI. Our results demonstrate that 60% correctness is the upper limit for a 4-type class prediction from amino acid composition alone for an unknown query protein and that consideration of compositional coupling does not improve the prediction success. The prediction program SSCP offering secondary structural class assignment for query compositions and sequences has been made available as a World Wide Web and E-mail service.

CT Check Tags: Comparative Study; Support, Non-U.S. Gov't

\*Amino Acids: CH, chemistry

**Computer Simulation**

Forecasting: MT, methods

**Models, Chemical**

**\*Protein Structure, Secondary**

CN 0 (Amino Acids)

L125 ANSWER 15 OF 19 MEDLINE

AN 96407679 MEDLINE

DN 96407679 PubMed ID: 8811732

TI Prediction of secondary structural content of proteins from their amino acid composition alone. I. New analytic vector decomposition methods.

AU Eisenhaber F; Imperiale F; Argos P; **Frommel C**

CS Institut fur Biochemie der Charite, Medizinische Fakultat, Humboldt-Universitat zu Berlin, Berlin-Mitte, Germany.

SO PROTEINS, (1996 Jun) 25 (2) 157-68.

Journal code: 8700181. ISSN: 0887-3585.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199612

ED Entered STN: 19970128

Last Updated on STN: 19970128

Entered Medline: 19961205

AB The predictive limits of the amino acid composition for the secondary structural content (percentage of residues in the secondary structural states helix, sheet, and coil) in proteins are assessed quantitatively. For the first time, techniques for prediction of secondary structural content are presented which rely on the amino acid composition as the only information on the query protein. In our first method, the amino acid composition of an unknown protein is represented by the best (in a least square sense) linear combination of the characteristic amino acid compositions of the three secondary structural types computed from a learning set of tertiary structures. The second technique is a generalization of the first one and takes into account also possible compositional couplings between any two sorts of amino acids. Its mathematical formulation results in an eigenvalue/eigenvector problem of the second moment matrix describing the amino acid compositional fluctuations of secondary structural types in various proteins of a learning set. Possible correlations of the principal directions of the eigenspaces with physical properties of the amino acids were also checked. For example, the first two eigenvectors of the helical eigenspace correlate with the size and hydrophobicity of the residue types respectively. As learning and test sets of tertiary structures, we utilized representative, automatically generated subsets of Protein Data Bank (PDB) consisting of non-homologous protein structures at the resolution thresholds  $\leq 1.8\text{\AA}$ ,  $\leq 2.0\text{\AA}$ ,  $\leq 2.5\text{\AA}$ , and  $\leq 3.0\text{\AA}$ . We show that the consideration of compositional couplings improves prediction accuracy, albeit not dramatically. Whereas in the self-consistency test (learning with the protein to be predicted), a clear



decrease of prediction accuracy with worsening resolution is observed, the jackknife test (leave the predicted protein out) yielded best results for the largest dataset (< or = 3.0A, almost no difference to the self-consistency test!), i.e., only this set, with more than 400 proteins, is sufficient for stable computation of the parameters in the prediction function of the second method. The average absolute error in predicting the fraction of helix, sheet, and coil from amino acid composition of the query protein are 13.7, 12.6, and 11.4%, respectively with r.m.s. deviations in the range of 8.6 divided by 11.8% for the 3.0 A dataset in a jackknife test. The absolute precision of the average absolute errors is in the range of 1 divided by 3% as measured for other representative subsets of the PDB. Secondary structural content prediction methods found in the literature have been clustered in accordance with their prediction accuracies. To our surprise, much more complex secondary structure prediction methods utilized for the same purpose of secondary structural content prediction achieve prediction accuracies very similar to those of the present analytic techniques, implying that all the information beyond the amino acid composition is, in fact, mainly utilized for positioning the secondary structural state in the sequence but not for determination of the overall number of residues in a secondary structural type. This result implies that higher prediction accuracies cannot be achieved relying solely on the amino acid composition of an unknown query protein as prediction input. Our prediction program SSCP has been made available as a World Wide Web and E-mail service.

CT Check Tags: Comparative Study; Support, Non-U.S. Gov't

\*Amino Acids: CH, chemistry

**Computer Simulation**

Forecasting: MT, methods

**Models, Chemical**

**\*Protein Structure, Secondary**

Reproducibility of Results

CN 0 (Amino Acids)

L125 ANSWER 16 OF 19 MEDLINE

AN 96190961 MEDLINE

DN 96190961 PubMed ID: 8609611

TI The automatic search for ligand binding sites in proteins of known three-dimensional structure using only geometric criteria.

AU Peters K P; Fauck J; Frommel C

CS Humboldt-University of Berlin, Medical Faculty (Charite), Institute of Biochemistry, Germany.

SO JOURNAL OF MOLECULAR BIOLOGY, (1996 Feb 16) 256 (1) 201-13.

Journal code: 2985088R. ISSN: 0022-2836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199605

ED Entered STN: 19960605

Last Updated on STN: 19960605

Entered Medline: 19960524

AB The biological function of a protein typically depends on the structure of specific binding sites. These sites are located at the surface of the protein molecule and are determined by geometrical arrangements and physico-chemical properties of tens of non-hydrogen atoms. In this paper we describe a new algorithm called APROPOS, based purely on geometric criteria for identifying such binding sites using atomic co-ordinates. For the description of the protein shape we use an alpha-shape algorithm which generates a whole family of shapes with different levels of detail. Comparing shapes of different resolution we find cavities on the surface of the protein responsible for ligand binding. The algorithm correctly locates more than 95% of all binding sites for ligands and prosthetic groups of molecular mass between about 100 and 2000 Da in a representative

set of proteins. Only in very few proteins does the method find binding sites of single ions outside the active site of enzymes. With one exception, we observe that interfaces between subunits show different geometric features compared to binding sites of ligands. Our results clearly support the view that protein-protein interactions occur between flat areas of protein surface whereas specific interactions of smaller ligands take place in pockets in the surface.

CT Check Tags: Animal; In Vitro; Support, Non-U.S. Gov't

Algorithms

Amino Acid Sequence

#### Binding Sites

Carrier Proteins: CH, chemistry

Carrier Proteins: GE, genetics

Carrier Proteins: ME, metabolism

DNA-Binding Proteins: CH, chemistry

DNA-Binding Proteins: GE, genetics

DNA-Binding Proteins: ME, metabolism

Databases, Factual

Heat-Shock Proteins: CH, chemistry

Heat-Shock Proteins: GE, genetics

Heat-Shock Proteins: ME, metabolism

Ligands

Models, Molecular

Molecular Sequence Data

Molecular Structure

Molecular Weight

#### Protein Binding

Protein Conformation

\*Proteins: CH, chemistry

Proteins: GE, genetics

Proteins: ME, metabolism

Pyrophosphatases: CH, chemistry

Pyrophosphatases: GE, genetics

Pyrophosphatases: ME, metabolism

Subtilisins: CH, chemistry

Subtilisins: GE, genetics

Subtilisins: ME, metabolism

Tacrolimus: ME, metabolism

Tacrolimus Binding Proteins

RN 109581-93-3 (Tacrolimus)

CN 0 (Carrier Proteins); 0 (DNA-Binding Proteins); 0 (Heat-Shock Proteins); 0 (Ligands); 0 (Proteins); EC 3.4.21.- (Subtilisins); EC 3.6.1.- (Pyrophosphatases); EC 3.6.1.1 (inorganic pyrophosphatase); EC 5.2.1.- (Tacrolimus Binding Proteins)

L125 ANSWER 17 OF 19 MEDLINE

AN 96180020 MEDLINE

DN 96180020 PubMed ID: 8609628

TI An evolutionary trace method defines binding surfaces common to protein families.

AU Lichtarge O; Bourne H R; Cohen F E

CS Department of Cellular and Molecular Pharmacology, University of California San Francisco, 94143-0450, USA.

SO JOURNAL OF MOLECULAR BIOLOGY, (1996 Mar 29) 257 (2) 342-58.

Journal code: 2985088R. ISSN: 0022-2836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Space Life Sciences

EM 199605

ED Entered STN: 19960605

Last Updated on STN: 19960605

Entered Medline: 19960530

AB X-ray or NMR structures of proteins are often derived without their **ligands**, and even when the structure of a full complex is available, the area of contact that is functionally and energetically significant may be a specialized subset of the geometric interface deduced from the spatial proximity between **ligands**. Thus, even after a structure is solved, it remains a major theoretical and experimental goal to localize protein functional interfaces and understand the role of their constituent residues. The evolutionary trace method is a systematic, transparent and novel predictive technique that identifies active sites and functional interfaces in proteins with known structure. It is based on the extraction of functionally important residues from sequence conservation patterns in homologous proteins, and on their mapping onto the protein surface to generate clusters identifying functional interfaces. The SH2 and SH3 modular signaling domains and the DNA binding domain of the nuclear hormone receptors provide tests for the accuracy and validity of our method. In each case, the evolutionary trace delineates the functional epitope and identifies residues critical to binding specificity. Based on mutational evolutionary analysis and on the structural homology of protein families, this simple and versatile approach should help focus site-directed mutagenesis studies of structure-function relationships in macromolecules, as well as studies of specificity in molecular recognition. More generally, it provides an evolutionary perspective for judging the functional or structural role of each residue in protein structure.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

**Amino Acid Sequence**

**\*Binding Sites**

**Conserved Sequence**

**DNA-Binding Proteins: CH, chemistry**

**Databases, Factual**

**\*Evolution, Molecular**

**Models, Molecular**

**Molecular Sequence Data**

**Mutation**

**Protein Conformation**

**\*Proteins: CH, chemistry**

**Rats**

**Receptors, Glucocorticoid: CH, chemistry**

**Sequence Alignment: MT, methods**

**Sequence Homology, Amino Acid**

**Zinc Fingers**

**src Homology Domains**

CN 0 (DNA-Binding Proteins); 0 (Proteins); 0 (Receptors, Glucocorticoid)

L125 ANSWER 18 OF 19 MEDLINE

AN 96038917 MEDLINE

DN 96038917 PubMed ID: 7584434

TI Constituting a receptor-ligand information base from quality-enriched data.

AU Hemm K; Aberer K; Hendlich M

CS GMD-IPSI, Darmstadt, Germany.

SO ISMB, (1995) 3 170-8.

Journal code: 9509125.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199512

ED Entered STN: 19960124

Last Updated on STN: 19960124

Entered Medline: 19951205

AB Many different resources are needed for analyzing relevant experimental

data in drug design. Currently this data is difficult to access, because it is stored in heterogeneous databases, spread over many platforms, poorly interconnected, incomplete, erroneous, or just not electronically available. In order to establish a high quality database for drug design we have developed a new demand-driven methodology for integrating and semantically enriching heterogeneous data from different research areas and for migrating the data into an object-oriented database management system. In this way we have established a database containing well-prepared, relevant data needed for drug design and offering the advantages of modern database technology, like a comprehensive object-oriented data model, a flexible declarative query language and support for persistent storage and sharing of data in a multi-user environment.

CT Check Tags: Comparative Study; Support, Non-U.S. Gov't

Amino Acid Sequence

Binding Sites

\*Computer Simulation

\*Databases, Factual

Drug Design

\*Ligands

Molecular Sequence Data

Protein Structure, Secondary

\*Proteins: CH, chemistry

\*Proteins: ME, metabolism

\*Receptors, Cell Surface: CH, chemistry

\*Receptors, Cell Surface: ME, metabolism

\*Receptors, Drug: CH, chemistry

\*Receptors, Drug: ME, metabolism

Sequence Homology, Amino Acid

CN 0 (Ligands); 0 (Proteins); 0 (Receptors, Cell Surface); 0 (Receptors, Drug)

L125 ANSWER 19 OF 19 MEDLINE

AN 95327685 MEDLINE

DN 95327685 PubMed ID: 7604031

TI Alternate protein frameworks for molecular recognition.

AU Ku J; Schultz P G

CS Howard Hughes Medical Institute, University of California, Berkeley 94720, USA.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Jul 3) 92 (14) 6552-6.

Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199508

ED Entered STN: 19950822

Last Updated on STN: 19980206

Entered Medline: 19950810

AB In an effort to determine whether proteins with structures other than the immunoglobulin fold can be used to mimic the **ligand** binding properties of antibodies, we generated a library from the four-helix bundle protein cytochrome b562 in which the two loops were randomized. Panning of this library against the bovine serum albumin (BSA) conjugate of N-methyl-p-nitrobenzylamine derivative 1 by phage display methods yielded cytochromes in which residues Trp-20, Arg-21, and Ser-22 in loop A and Arg-83 and Trp-84 in loop B were conserved. The individual mutants, which fold into native-like structure, bind selectively to the BSA-1 conjugate with micromolar dissociation constants (Kd), in comparison to a monoclonal antibody that binds selectively to 1 with a Kd of 290 nM. These and other antibody-like receptors may prove useful as therapeutic agents or as reagents for both intra- and extracellular studies.